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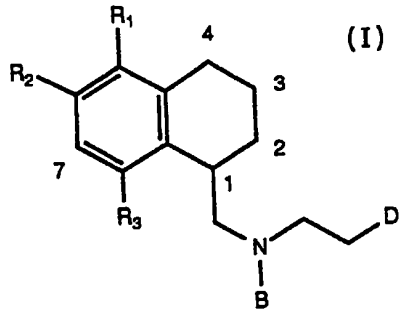

(57) Abstract

The present invention provides an amine compound of formula (I) or a pharmaceutically acceptable salt thereof which is an antagonist for alpha-2 adrenoreceptors and which inhibits serotonin (5-hydroxytryptamine, 5-HT) uptake.

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TERTIARY AND SECONDARY AMINES AS ALPHA-2 ANTAGONISTS AND SEROTONIN UPTAKE INHIBITORS

Technical Field

The present invention relates to novel organic compounds and compositions which are both alpha-2 adrenoreceptor antagonists and serotonin (5-hydroxytryptamine, 5-HT) uptake inhibitors, processes for making such compounds, synthetic intermediates employed in these processes, and a method for treating diseases of the central nervous system including depression, aggression, obsessive compulsive disorders, panic attacks, memory disturbances, anxiety, hypochondriasis, and aspects of Alzheimer's disease, diseases of the vascular system including hypertension, glaucoma and migraine, metabolic disorders such as diabetes or feeding disorders, and alcoholism.

Background of the Invention

There is evidence that the pathophysiology of depression and anxiety disorders is related to some type of serotonin dysfunction. The tricyclic antidepressant imipramine binds with high affinity to a recognition site associated with the transport of 5-HT. The site at which these tricyclic antidepressants bind is not identical to the 5-HT binding site and yet binding of compounds of this type inhibits the uptake of 5-HT (serotonin); an allosteric relationship is postulated (Charney, D.S., Krystal, J.H., Delgado, P.L., Heninger, G.R., *Annu. Rev. Med.* **1990**, *41*: 437). A number of compounds which demonstrate highly selective serotonin uptake inhibition have shown clinical efficacy as antidepressants (Fuller, R.W., Wong, D.T., *Ann. N.Y. Acad. Sci.*, **1990**, *600*: 68). It has been found that serotonin uptake inhibitors bind with less affinity to neurotransmitter receptors than the tricyclic antidepressants; this lower binding affinity is thought to be responsible for fewer chlorinergic and histaminergic side effects for these uptake inhibitors (Robertson, D.W., Fuller, R.W., *Ann. Rep. Med. Chem.*, **1991**, *26*: 23) relative to the tricyclic antidepressants.

Serotonin uptake inhibitors are thought to offer clinical advantages over the tricyclic antidepressants because they exhibit fewer severe adverse drug reactions, particularly as far as cardiovascular side effects and overdose potential. Serotonin uptake inhibitors have shown some indications of efficacy in the treatment of obsessive compulsive disorder (Zak, J., Miller, J., Sheehan, D., Fanous, B., *J.*

Clin. Psychiatry, **1990**, *49*: 23), panic disorders (Balon, R., Pohl, R.I., Yergani, V., Rainey, J., Oxenkrug, G., *Acta. Psychiatr. Scand.*, **1987**, *75*: 315), alchoholism (Gill, K., Amit, Z., Koe, K., *Alcohol*, **1988**, 349), and feeding disorders (Wong, D., Fuller, R., *Int. J. Obesity*, **1987**, *11*: 125). Some of the emotional aspects of Alzheimer's disease were ameliorated by the use of a serotonin uptake inhibitor (Karlsson, I., *Clinical Neuropharmacol.*, **1990**, *13 (Suppl 2)*: 99). There is some indication that the serotonin uptake inhibitor Fluoxetine is effective in the treatment of hypochondriasis (Viswanathan, R., Paradis, C., *Am. J. Psychiatr.*, **1991**, *148*: 1090).

The adrenergic nervous system plays a major role in the innervation of heart, blood vessel and smooth muscle tissue. Compounds capable of interacting with receptor sites within the adrenergic nervous system can initiate a variety of physiological responses, including vasoconstriction, vasodilation, and increased or decreased heart rate (chronotropic), contractility (inotropic) and metabolic activity. In the past, various adrenergic compounds have been employed to affect these and other physiological responses. However, many adrenergic compounds do not possess significant selectivity to enable desirable interactions with adrenergic receptor sites. That is, these adrenergic compounds do not demonstrate a high degree of specificity for differing receptors types within the adrenergic nervous system in order to obtain a desired physiological response separate from other possible, and perhaps less desirable, responses of the system.

The fact that adrenergic and serotonergic nerve terminals exist in close proximity in various brain regions might indicate some kind of functional interaction between these two neurotransmitter systems. There is evidence that presynaptic alpha-2 adrenergic receptors are located on 5-HT nerve terminals where they function to inhibit the release of 5-HT (Gothert, M., Huth, H., *Naunyn-Schmiedeberg's Arch. Pharmacol.*, **1980**, *313*: 21 and Gothert, M., Huth, H., Schlicker, E., *Naunyn-Schmiedeberg's Arch. Pharmacol.*, **1981**, *317*: 199). It has been demonstrated in *in vitro* slice preparations that alpha-2 antagonists are capable of reversing the inhibition of 5-HT release upon electrical stimulation under quasi physiological conditions by either exogenously applied alpha-2 agonists or endogenous norepinephrine (NE) (Charney, D.S., Krystal, J.H., Delgado, P.L. Heninger, G.R., *Annu. Rev. Med.* **1990**, *41*: 437). One might therefore conclude that an agent which combines alpha-2 antagonist activity with 5-HT uptake inhibitory activity would be more effective than either activity alone in increasing the biophase concentration of 5-HT. Compounds such as napamezole, Win 51181-2,

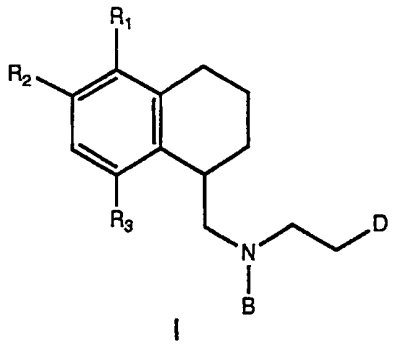
which is a potent and selective alpha-2 adrenergic receptor antagonist and also inhibits serotonin (5-hydroxytryptamine, 5-HT) uptake, is under development by Sterling Drug as an antidepressant (*Pharma Projects*, May **1991**, 12). Chronic uptake blockade will, over time, result in down-regulation of the alpha-2 receptor, and perhaps the delay in onset of antidepressant efficacy correlates with the time required for receptor down-regulation.

1-Aminomethyl-1,2,3,4-tetrahydronaphthalenes have been described by J.F. DeBernardis, R.E. Zelle and F.Z. Basha in International Patent Application Number WO 89/06645. One of their generic structures encompasses methylenedioxy and ethylenedioxy heterocyclic compounds which are excluded from the present invention. Their compounds do not possess the selective alpha-2 antagonist activity with the inhibition of serotonin uptake profile of the present compounds.

Summary of the Invention

The compounds of the present invention demonstrate the ability to selectively inhibit serotonin (5-hydroxytryptamine, 5-HT) uptake and alpha-2 adrenergic receptors, *i.e.* are alpha-2 antagonists, which are mainly distributed on the membranes of central and peripheral adrenergic neurons and on the tissues innervated thereby. By inhibiting interaction with the alpha-adrenergic receptors in the peripheral nervous system, one can modulate the function of adrenergic neurons and hemodynamic equilibrium which is therapeutically useful in a multitude of cardiovascular indications, such as hypertension, congestive heart failure, and a variety of vascular spastic conditions. Furthermore, the alpha-adrenergic antagonists are useful in certain neurological and psychiatric disorders such as depression. Dual pharmacophores which are alpha-2 antagonists and also inhibit the uptake of serotonin would be anticipated to have a beneficial synergistic effect with enhanced efficacy over each type of activity alone, the potential for faster onset of action and/or efficacy among non-responding patients while perhaps having a desirable side effect profile.

In accordance with the principal embodiment of the present invention, there are provided alpha-2 adrenoreceptor antagonists and serotonin (5-hydroxy-tryptamine, 5-HT) uptake inhibiting compounds of the formula I:

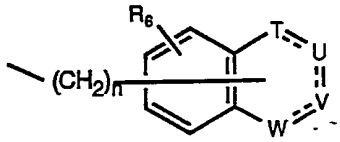


I

and the pharmaceutically acceptable salts thereof. In the above formula R_1 is alkoxy of from one to four carbon atoms, R_2 is hydrogen or taken together with R_1 is methylenedioxy or ethylenedioxy, and R_3 is hydrogen, fluorine, or chlorine.

The substituent B is hydrogen or alkyl of from one to three carbon atoms.

The residue D is selected from



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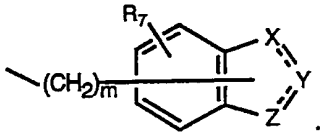
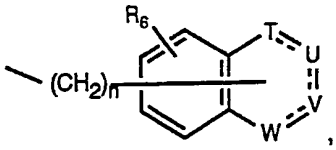


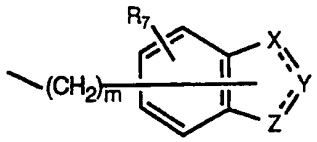
When D is



then n is 0, 1, or 2, and T, U, V, and W represent $>CH_2$, =CH-, >C=O, >O, >N-R_8 and =N-, and >S, >S(O), and $>SO_2$. The dotted lines represent optional double bonds and R_8 is hydrogen, alkyl of from one to four atoms, or alkylsulfonyl. R_6 is one, two, or three substituents independently selected from hydrogen, alkyl of from one to four carbon atoms, halogen, hydroxy, alkoxy of from one to four carbon atoms, amino, and thioalkoxy of from one to four carbon atoms. The following

provisos apply: (a) when there is a double bond between T and U and/or V and W, then there cannot be a double bond between U and V, (b) not more than three of T, U, V, and W are nitrogen, (c) not more than two of T, U, V, and W are oxygen, and then not in contiguous positions, (d) not more than two of T, U, V, and W are sulfur, and (e) not more than two of T, U, V, and W are >C=O.

Alternatively, when D is



then m is 0, 1, or 2, and X, Y, and Z are independently selected from CH_2, =CH-, >C=O, >O, >N-R_8 and =N-, and >S, >S(O), and >SO_2. The dotted lined represent optional double bonds, and R_8 is hydrogen, alkyl of from one to four atoms, or alkylsulfonyl. R_7 is one, two, or three substituents independently selected from the group consisting of hydrogen, alkyl of from one to four carbon atoms, halogen, hydroxy, alkoxy of from one to four carbon atoms, amino, and thioalkoxy of from one to four carbon atoms. The following provisos apply: (f) there may be only one double bond between either X and Y or between Y and Z, (g) not more than one of X, Y, and Z is oxygen, (h) not more than two of X, Y, and Z are sulfur, and (i) not more than two of X, Y, and Z are >C=O.

The pharmaceutically acceptable salts and individual stereoisomers of compounds of structural formula I above, as well as mixtures thereof, are also contemplated as falling within the scope of the present invention.

In another aspect, the present invention also relates to a method for antagonizing alpha-2 adrenoreceptor activity and inhibiting 5-hydroxytryptamine uptake in a mammal in need of such treatment, comprising administering to the mammal a therapeutically effective amount of a compound of Claim 1.

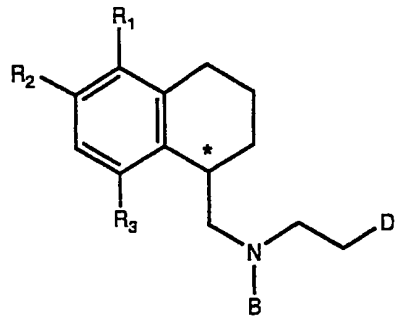
In yet another aspect, the present invention also relates to processes for making such compounds and the synthetic intermediates employed in these processes.

The invention further relates to alpha-2 adrenoreceptor antagonist and 5-hydroxytryptamine uptake inhibiting compositions comprising a pharmaceutical carrier and a therapeutically effective amount of a compound of Claim 1.

In yet another aspect of the present invention, there is provided a method of treating diseases of the central nervous system including depression, agression, obsessive compulsive disorders, panic attacks, hypochondriasis, memory disturbances, and anxiety, diseases of the vascular system including hypertension, glaucoma and migraine, metabolic disorders such as diabetes or feeding disorders, and alcoholism by administering to a host mammal in need of such treatment a therapeutically effective amount of a compound of Claim 1.

Detailed Description of the Invention

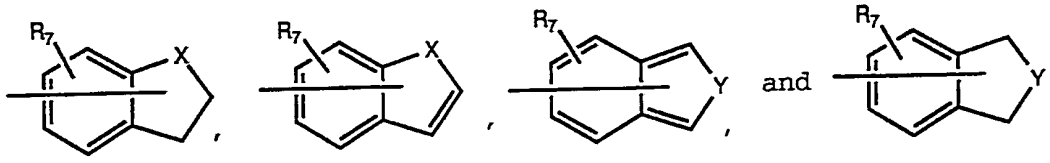
In a preferred embodiment of the present invention, compounds are represented by Formula Ia:



Ia

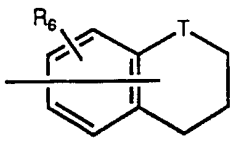
wherein B, R_1, R_2, R_3, and D are as defined above and the stereochemistry at the asymmetric center (*) is of the R configuration.

Preferred embodiments of the compounds of this invention are those wherein B and R_7 are as defined above and D is selected from



X and Y are independently selected from $>CH_2$, >O, >S, >SO, $>SO_2$, and >N-R_8 where R_8 is selected from hydrogen, lower alkyl, and alkylsulfonyl.

In another preferred embodiment, B and R_6 are as defined above and D is selected from



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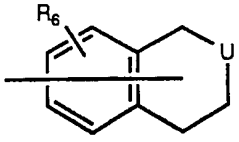
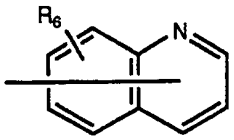


wherein T and U are independently selected from >CH_2, >O, >S, >SO, >SO_2, and >N-R_8 where R_8 is selected from hydrogen, lower alkyl, and alkylsulfonyl.

In another preferred embodiment, B and R_6 are as defined above and D is selected from



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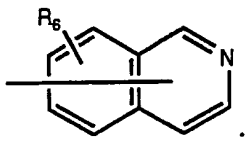
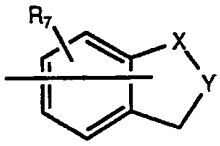


In another preferred embodiment, B and R_7 are as defined above and D is selected from



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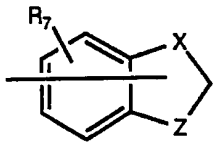
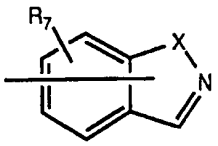


wherein X, Y and Z are independently selected from >O, >S, >SO, >SO_2, and >N-R_8 where R_8 is selected from hydrogen, lower alkyl, and alkylsulfonyl wherein not both X and Z are oxygen.

In another embodiment, B and R_7 are as defined above and D is selected from



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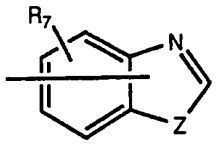
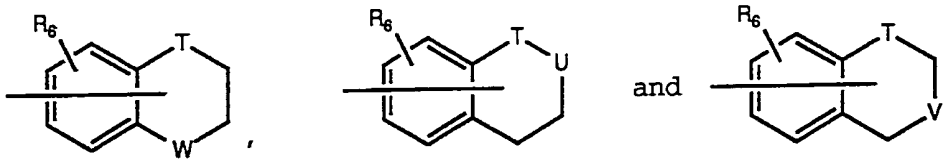


wherein X and Z are independently selected from >O, >S, >SO, >SO_2, and >N-R_8 where R_8 is selected from hydrogen, lower alkyl, and alkylsulfonyl.

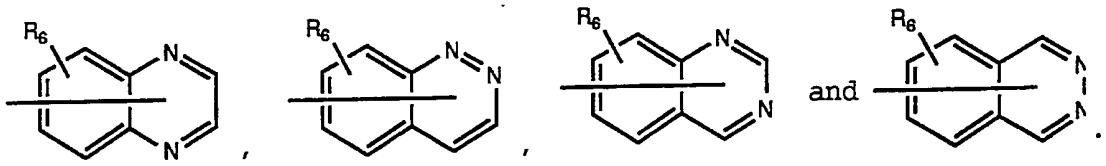
In another embodiment, B and R_6 are as defined above and D is selected from



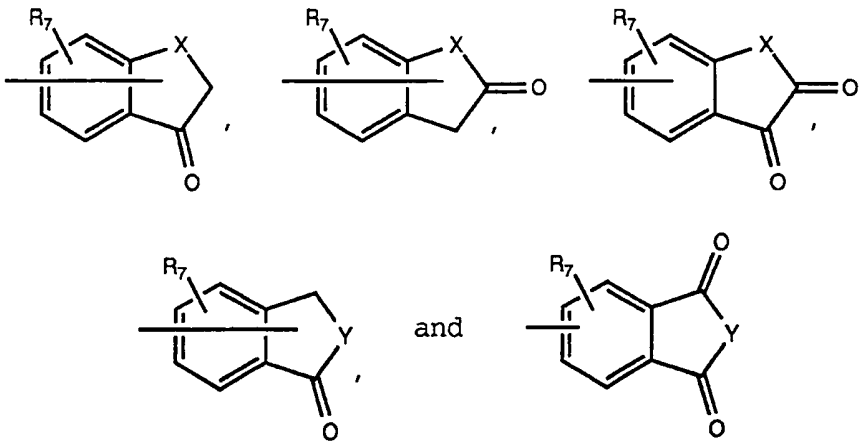
wherein T, U, V, and W are independently selected from >O, >S, >SO, >SO_2, and >N-R_8 where R_8 is selected from hydrogen, lower alkyl, and alkylsulfonyl with the provisos that 1) T and U cannot both be oxygen and 2) T and W cannot both be oxygen.

In another embodiment, B and R_6 are as defined above and D is selected from

In another embodiment, B and R_6 are as defined above and D is selected from

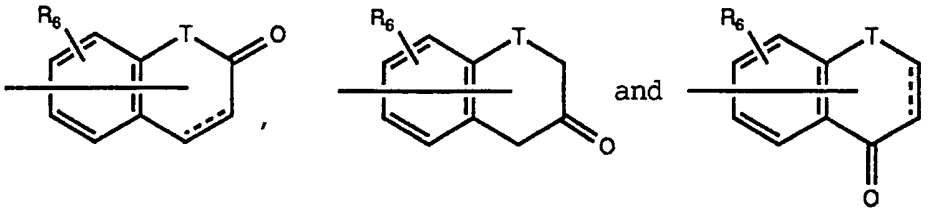


In another embodiment, B and R_7 are as defined above and D is selected from the group consisting of



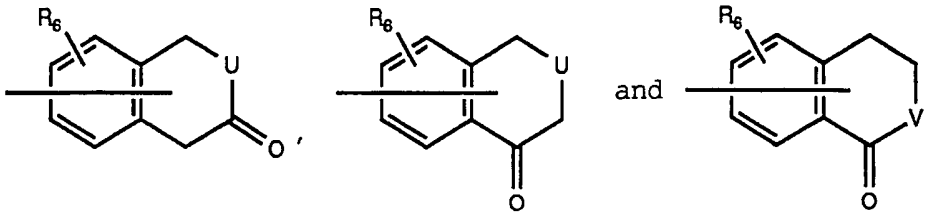
wherein X and Y are independently selected from >O, >S, >SO, >SO_2, and >N-R_8 where R_8 is selected from hydrogen, lower alkyl, and alkylsulfonyl.

In another embodiment, B and R_6 are as defined above and D is selected from



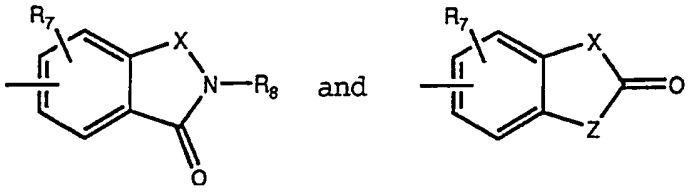
wherein T is independently selected from >O, >S, >SO, >SO_2, and >N-R_8 where R_8 is selected from hydrogen, lower alkyl, and alkylsulfonyl with optional double bonds as indicated by the dotted lines.

In another embodiment, B and R_6 are as defined above and D is selected from



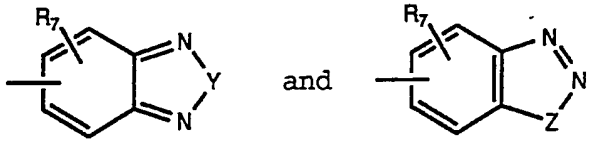
wherein U and V are independently selected from >O, >S, >SO, >SO_2, and >N-R_8 where R_8 is selected from hydrogen, lower alkyl, and alkylsulfonyl.

In another embodiment, B and R_7 are as defined above and D is selected from



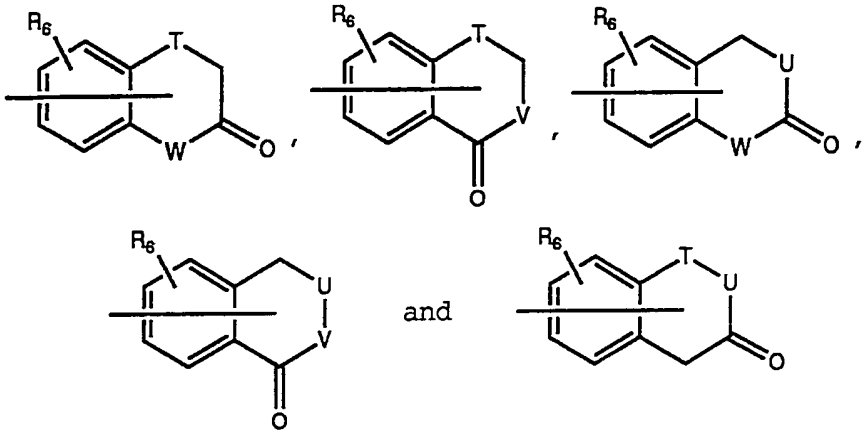
wherein X and Z are independently selected from >O, >S, >SO, $>SO_2$, and >N-R_8 where R_8 is selected from hydrogen, lower alkyl, and alkylsulfonyl.

In another embodiment, B and R_7 are as defined above and D is selected from



wherein Y and Z are independently selected from >C=O, >O, >S, >SO, $>SO_2$, and >N-R_8 where R_8 is selected from hydrogen, lower alkyl, and alkylsulfonyl.

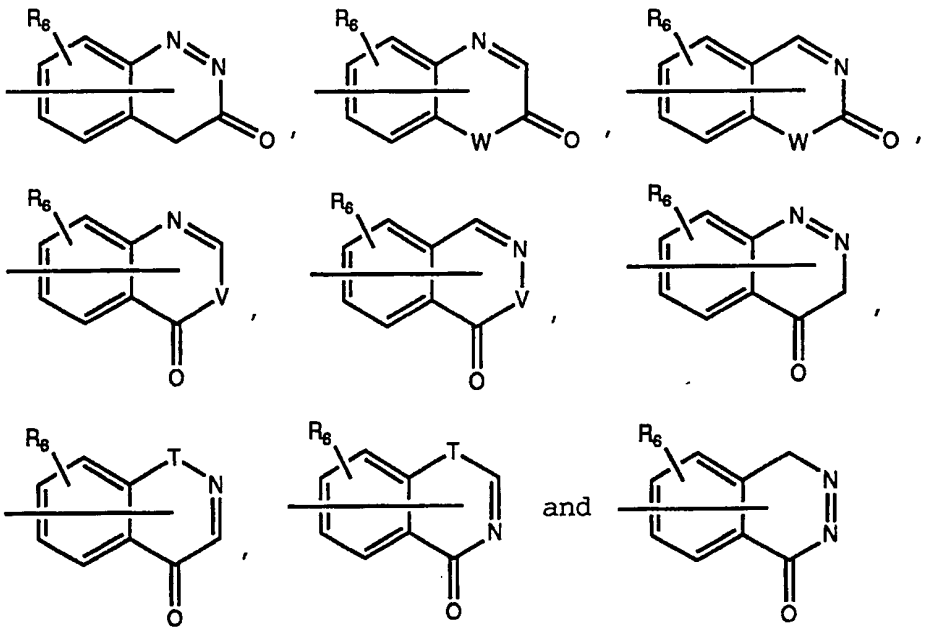
In another embodiment, B and R_6 are as defined above and D is selected from the group consisting of



wherein T,U, V, and W are independently selected from >C=O, >O, >S, >SO, $>SO_2$, and >N-R_8 where R_8 is selected from hydrogen, lower alkyl, and

alkylsulfonyl with the provisos that only one of T, U, V, and W is >C=O and only nitrogen heteroatoms may be adjacent to each other.

In another embodiment, B and R_6 are as defined above and D is selected from the group consisting of



wherein T, V, and W are independently selected from >C=O, >O, >S, >SO, $>SO_2$, and >N-R_8 where R_8 is selected from hydrogen, lower alkyl, and alkylsulfonyl with the provisos that only one of T, V, and W is >C=O and only nitrogen heteroatoms may be adjacent to each other.

Examples of compounds falling within the scope of the present invention include, but are not limited to, the following:

N-[2-(2,3-Dihydro-benzo[b]thiophen-6-yl)-ethyl]-N-(5-methoxy-1,2,3,4-tetrahydro-naphthalen-1-ylmethyl)-N-methylamine;

N-[2-(3H-Inden-5-yl)-ethyl]-N-(5-methoxy-1,2,3,4-tetrahydro-naphthalen-1-ylmethyl)-N-methylamine;

N-[2-(1H-Indol-5-yl)-ethyl]-N-(5-methoxy-1,2,3,4-tetrahydro-naphthalen-1-ylmethyl)-N-methylamine;

N-(2-Benzo[b]thiophen-5-yl-ethyl)-N-(5-methoxy-1,2,3,4-tetrahydro-naphthalen-1-ylmethyl)-N-methylamine;

N-[2-(2H-Isoindol-5-yl)-ethyl]-N-(5-methoxy-1,2,3,4-tetrahydro-naphthalen-1-ylmethyl)-N-methylamine;

N-(2-Isobenzofuran-5-yl)-ethyl)-N-(5-methoxy-1,2,3,4-tetrahydro-naphthalen-1-ylmethyl)-N-methylamine;

N-[2-(1,3-Dihydro-benzo[c]thiophen-5-yl)-ethyl]-N-(5-methoxy-1,2,3,4-tetrahydro-naphthalen-1-ylmethyl)-N-methylamine;

N-[2-(1,2,3,4-Tetrahydro-quinolin-7-yl)-ethyl]-N-(5-methoxy-1,2,3,4-tetrahydro-naphthalen-1-ylmethyl)-N-methylamine;

N-[2-(1,2,3,4-Tetrahydro-quinolin-6-yl)-ethyl]-N-(5-methoxy-1,2,3,4-tetrahydro-naphthalen-1-ylmethyl)-N-methylamine;

N-(2-Chroman-7-yl-ethyl)-N-(5-methoxy-1,2,3,4-tetrahydro-naphthalen-1-ylmethyl)-N-methylamine;

N-(2-Chroman-6-yl-ethyl)-N-(5-methoxy-1,2,3,4-tetrahydro-naphthalen-1-ylmethyl)-N-methylamine;

N-(2-Thiochroman-7-yl-ethyl)-N-(5-methoxy-1,2,3,4-tetrahydro-naphthalen-1-ylmethyl)-N-methylamine;

N-(2-Thiochroman-6-yl-ethyl)-N-(5-methoxy-1,2,3,4-tetrahydro-naphthalen-1-ylmethyl)-N-methylamine;

N-[2-(1,2,3,4-Tetrahydro-isoquinolin-7-yl)-ethyl]-N-(5-methoxy-1,2,3,4-tetrahydro-naphthalen-1-ylmethyl)-N-methylamine;

N-[2-(1,2,3,4-Tetrahydro-isoquinolin-6-yl)-ethyl]-N-(5-methoxy-1,2,3,4-tetrahydro-naphthalen-1-ylmethyl)-N-methylamine;

N-(2-Isochroman-7-yl-ethyl)-N-(5-methoxy-1,2,3,4-tetrahydro-naphthalen-1-ylmethyl)-N-methylamine;

N-(2-Isochroman-6-yl-ethyl)-N-(5-methoxy-1,2,3,4-tetrahydro-naphthalen-1-ylmethyl)-N-methylamine;

N-(2-Isothiochroman-7-yl-ethyl)-N-(5-methoxy-1,2,3,4-tetrahydro-naphthalen-1-ylmethyl)-N-methylamine;

N-(2-Isothiochroman-6-yl-ethyl)-N-(5-methoxy-1,2,3,4-tetrahydro-naphthalen-1-ylmethyl)-N-methylamine;

N-[2-(3H-Indol-5-yl-ethyl)-N-(5-methoxy-1,2,3,4-tetrahydro-naphthalen-1-ylmethyl)-N-methylamine;

N-[2-(3H-Indol-6-yl-ethyl)-N-(5-methoxy-1,2,3,4-tetrahydro-naphthalen-1-ylmethyl)-N-methylamine;

N-[2-(3H-Isoindol-5-yl-ethyl)-N-(5-methoxy-1,2,3,4-tetrahydro-naphthalen-1-ylmethyl)-N-methylamine;

N-[2-(3H-Isoindol-6-yl-ethyl)-N-(5-methoxy-1,2,3,4-tetrahydro-naphthalen-1-ylmethyl)-N-methylamine;

N-[2-(1H-Indazol-5-yl)-ethyl]-N-(5-methoxy-1,2,3,4-tetrahydro-naphthalen-1-ylmethyl)-N-methylamine;

N-[2-(1H-Indazol-6-yl)-ethyl]-N-(5-methoxy-1,2,3,4-tetrahydro-naphthalen-1-ylmethyl)-N-methylamine;

N-[2-(2,3-Dihydro-1H-benzoimidazol-5-yl)ethyl]-N-(5-methoxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl)-N-methylamine;

N-[2-(2,3-Dihydro-benzothiazol-5-yl)ethyl]-N-(5-methoxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl)-N-methylamine;

N-[2-(2,3-Dihydro-benzoxazol-5-yl)ethyl]-N-(5-methoxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl)-N-methylamine;

N-[2-(1,3-Dihydro-benzo[c]isothiazol-5-yl)ethyl]-N-(5-methoxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl)-N-methylamine;

N-[2-(3H-Benzo[d][1,2]oxathiol-5-yl)ethyl]-N-(5-methoxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl)-N-methylamine;

N-[2-(1,3-Dihydro-benzo[c]isoxazol-5-yl)ethyl]-N-(5-methoxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl)-N-methylamine;

N-[2-(2,3-Dihydro-benzo[d]isothiazol-5-yl)ethyl]-N-(5-methoxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl)-N-methylamine;

N-[2-(2,3-Dihydro-benzo[d]isoxazol-5-yl)ethyl]-N-(5-methoxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl)-N-methylamine;

N-[2-(2,3-Dihydro-1H-indazol-5-yl)ethyl]-N-(5-methoxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl)-N-methylamine;

N-(2-Benzo[d]isoxazol-6-yl-ethyl)-N-(5-methoxy-1,2,3,4-tetrahydro-naphthalen-1-ylmethyl)-N-methylamine;

N-(2-Benzo[d]isothiazol-6-yl-ethyl)-N-(5-methoxy-1,2,3,4-tetrahydro-naphthalen-1-ylmethyl)-N-methylamine;

N-(2-Benzo[1,3]dithiol-5-yl)-ethyl]-N-(5-methoxy-1,2,3,4-tetrahydro-naphthalen-1-ylmethyl)-N-methylamine;

N-(2-Benzo[1,3]oxathiol-6-yl)-ethyl]-N-(5-methoxy-1,2,3,4-tetrahydro-naphthalen-1-ylmethyl)-N-methylamine;

N-[2-(1,2,3,4-Tetrahydro-quinoxalin-6-yl)-ethyl]-N-(5-methoxy-1,2,3,4-tetrahydro-naphthalen-1-ylmethyl)-N-methylamine;

N-[2-(1,4-Benzodioxan-6-yl)-ethyl]-N-(5-methoxy-1,2,3,4-tetrahydro-naphthalen-1-ylmethyl)-N-methylamine;

N-[2-(1,4-Benzodithian-6-yl)-ethyl]-N-(5-methoxy-1,2,3,4-tetrahydro-naphthalen-1-ylmethyl)-N-methylamine;

N-[2-(3,4-Dihydro-2H-benzo[1,4]oxazin-6-yl)-ethyl]-N-(5-methoxy-1,2,3,4-tetrahydro-naphthalen-1-ylmethyl)-N-methylamine;

N-[2-(3,4-Dihydro-2H-benzo[1,4]oxazin-7-yl)-ethyl]-N-(5-methoxy-1,2,3,4-tetrahydro-naphthalen-1-ylmethyl)-N-methylamine;

N-[2-(3,4-Dihydro-2H-benzo[1,4]thiazin-6-yl)-ethyl]-N-(5-methoxy-1,2,3,4-tetrahydro-naphthalen-1-ylmethyl)-N-methylamine;

N-[2-(3,4-Dihydro-2H-benzo[1,4]thiazin-7-yl)-ethyl]-N-(5-methoxy-1,2,3,4-tetrahydro-naphthalen-1-ylmethyl)-N-methylamine;

N-[2-(2,3-Dihydro-benzo[1,4]oxathiin-6-yl)-ethyl]-N-(5-methoxy-1,2,3,4-tetrahydro-naphthalen-1-ylmethyl)-N-methylamine;

N-[2-(3,4-Dihydro-2H-benzo[1,4]oxathiin-7-yl)-ethyl]-N-(5-methoxy-1,2,3,4-tetrahydro-naphthalen-1-ylmethyl)-N-methylamine;

N-[2-(1,2,3,4-Tetrahydro-cinnolin-7-yl)-ethyl]-N-(5-methoxy-1,2,3,4-tetrahydro-naphthalen-1-ylmethyl)-N-methylamine;

N-[2-(1,2,3,4-Tetrahydro-cinnolin-6-yl)-ethyl]-N-(5-methoxy-1,2,3,4-tetrahydro-naphthalen-1-ylmethyl)-N-methylamine;

N-[2-(3,4-Dihydro-benzo[c][1,2]dithiin-6-yl)-ethyl]-N-(5-methoxy-1,2,3,4-tetrahydro-naphthalen-1-ylmethyl)-N-methylamine;

N-[2-(3,4-Dihydro-benzo[c][1,2]dithiin-7-yl)-ethyl]-N-(5-methoxy-1,2,3,4-tetrahydro-naphthalen-1-ylmethyl)-N-methylamine;

N-[2-(1,2,3,4-Tetrahydro-quinazolin-7-yl)-ethyl]-N-(5-methoxy-1,2,3,4-tetrahydro-naphthalen-1-ylmethyl)-N-methylamine;

N-[2-(1,2,3,4-Tetrahydro-quinazolin-6-yl)-ethyl]-N-(5-methoxy-1,2,3,4-tetrahydro-naphthalen-1-ylmethyl)-N-methylamine;

N-[2-(1,3-Benzodioxan-7-yl)-ethyl]-N-(5-methoxy-1,2,3,4-tetrahydro-naphthalen-1-ylmethyl)-N-methylamine;

N-[2-(1,3-Benzodioxan-6-yl)-ethyl]-N-(5-methoxy-1,2,3,4-tetrahydro-naphthalen-1-ylmethyl)-N-methylamine;

N-[2-(1,3-Benzodithian-7-yl)-ethyl]-N-(5-methoxy-1,2,3,4-tetrahydro-naphthalen-1-ylmethyl)-N-methylamine;

N-[2-(1,3-Benzodithian-6-yl)-ethyl]-N-(5-methoxy-1,2,3,4-tetrahydro-naphthalen-1-ylmethyl)-N-methylamine;

N-[2-(4H-Benzo[d][1,3]oxathiin-7-yl)-ethyl]-N-(5-methoxy-1,2,3,4-tetrahydro-naphthalen-1-ylmethyl)-N-methylamine;

N-[2-(4H-Benzo[d][1,3]oxathiin-6-yl)-ethyl]-N-(5-methoxy-1,2,3,4-tetrahydro-naphthalen-1-ylmethyl)-N-methylamine;

N-[2-(1,4-Dihydro-2H-benzo[d][1,3]thiazin-7-yl)-ethyl]-N-(5-methoxy-1,2,3,4-tetrahydro-naphthalen-1-ylmethyl)-N-methylamine;

N-[2-(1,4-Dihydro-2H-benzo[d][1,3]thiazin-6-yl)-ethyl]-N-(5-methoxy-1,2,3,4-tetrahydro-naphthalen-1-ylmethyl)-N-methylamine;

N-[2-(1,4-Dihydro-2H-benzo[d][1,3]oxazin-7-yl)-ethyl]-N-(5-methoxy-1,2,3,4-tetrahydro-naphthalen-1-ylmethyl)-N-methylamine;

N-[2-(1,4-Dihydro-2H-benzo[d][1,3]oxazin-6-yl)-ethyl]-N-(5-methoxy-1,2,3,4-tetrahydro-naphthalen-1-ylmethyl)-N-methylamine;

N-[2-(3,4-Dihydro-2H-benzo[e][1,3]oxazin-7-yl)-ethyl]-N-(5-methoxy-1,2,3,4-tetrahydro-naphthalen-1-ylmethyl)-N-methylamine;

N-[2-(3,4-Dihydro-2H-benzo[e][1,3]oxazin-6-yl)-ethyl]-N-(5-methoxy-1,2,3,4-tetrahydro-naphthalen-1-ylmethyl)-N-methylamine;

N-(2-Cinnolin-7-yl-ethyl)-N-(5-methoxy-1,2,3,4-tetrahydro-naphthalen-1-ylmethyl)-N-methylamine;

N-(2-Cinnolin-6-yl-ethyl)-N-(5-methoxy-1,2,3,4-tetrahydro-naphthalen-1-ylmethyl)-N-methylamine;

N-(2-Quinazolin-7-yl-ethyl)-N-(5-methoxy-1,2,3,4-tetrahydro-naphthalen-1-ylmethyl)-N-methylamine;

N-(2-Quinazolin-6-yl-ethyl)-N-(5-methoxy-1,2,3,4-tetrahydro-naphthalen-1-ylmethyl)-N-methylamine;

N-(2-Phthalazin-6-yl-ethyl)-N-(5-methoxy-1,2,3,4-tetrahydro-naphthalen-1-ylmethyl)-N-methylamine;

6-{2-[(5-Methoxy-1,2,3,4-tetrahydro-naphthalen-1-ylmethyl)-methyl-amino]-ethyl}-bezofuranon-3-one;

6-{2-[(5-Methoxy-1,2,3,4-tetrahydro-naphthalen-1-ylmethyl)-methyl-amino]-ethyl}-1,2-dihydro-indol-3-one;

6-{2-[(5-Methoxy-1,2,3,4-tetrahydro-naphthalen-1-ylmethyl)-methyl-amino]-ethyl}-benzo[b]thiophen-3-one;

6-{2-[(5-Methoxy-1,2,3,4-tetrahydro-naphthalen-1-ylmethyl)-methyl-amino]-ethyl}-indan-1-one;

6-{2-[(5-Methoxy-1,2,3,4-tetrahydro-naphthalen-1-ylmethyl)-methyl-amino]-ethyl}-indan-2-one;

6-{2-[(5-Methoxy-1,2,3,4-tetrahydro-naphthalen-1-ylmethyl)-methyl-amino]-ethyl}-1,3-dihydro-indol-2-one;

6-{2-[(5-Methoxy-1,2,3,4-tetrahydro-naphthalen-1-ylmethyl)-methyl-amino]-ethyl}-3H-benzofuran-2-one;

6-{2-[(5-Methoxy-1,2,3,4-tetrahydro-naphthalen-1-ylmethyl)-methyl-amino]-ethyl}-3H-benzo[b]thiophen-2-one;

6-{2-[(5-Methoxy-1,2,3,4-tetrahydro-naphthalen-1-ylmethyl)-methyl-amino]-ethyl}-benzo[b]thiophen-2,3-dione;

6-{2-[(5-Methoxy-1,2,3,4-tetrahydro-naphthalen-1-ylmethyl)-methyl-amino]-ethyl}-benzofuran-2,3-dione;

6-{2-[(5-Methoxy-1,2,3,4-tetrahydro-naphthalen-1-ylmethyl)-methyl-amino]-ethyl}-1H-indole-2,3-dione;

5-{2-[(5-Methoxy-1,2,3,4-tetrahydro-naphthalen-1-ylmethyl)-methyl-amino]-ethyl}-indan-1,2-dione;

5-{2-[(5-Methoxy-1,2,3,4-tetrahydro-naphthalen-1-ylmethyl)-methyl-amino]-ethyl}-2,3-dihydro-isoindol-1-one;

5-{2-[(5-Methoxy-1,2,3,4-tetrahydro-naphthalen-1-ylmethyl)-methyl-amino]-ethyl}-3H-isobenzofuran-1-one;

5-{2-[(5-Methoxy-1,2,3,4-tetrahydro-naphthalen-1-ylmethyl)-methyl-amino]-ethyl}-3H-benzo[b]thiophen-1-one;

6-{2-[(5-Methoxy-1,2,3,4-tetrahydro-naphthalen-1-ylmethyl)-methyl-amino]-ethyl}-benzo[c]thiophen-1,3-one;

7-{2-[(5-Methoxy-1,2,3,4-tetrahydro-naphthalen-1-ylmethyl)-methyl-amino]-ethyl}-3,4-dihydro-1H-naphthalen-2-one;

6-{2-[(5-Methoxy-1,2,3,4-tetrahydro-naphthalen-1-ylmethyl)-methyl-amino]-ethyl}-3,4-dihydro-1H-naphthalen-2-one;

7-{2-[(5-Methoxy-1,2,3,4-tetrahydro-naphthalen-1-ylmethyl)-methyl-amino]-ethyl}-3,4-dihydro-1H-quinolin-2-one;

6-{2-[(5-Methoxy-1,2,3,4-tetrahydro-naphthalen-1-ylmethyl)-methyl-amino]-ethyl}-3,4-dihydro-1H-quinolin-2-one;

7-{2-[(5-Methoxy-1,2,3,4-tetrahydro-naphthalen-1-ylmethyl)-methyl-amino]-ethyl}-chroman-2-one;

6-{2-[(5-Methoxy-1,2,3,4-tetrahydro-naphthalen-1-ylmethyl)-methyl-amino]-ethyl}-chroman-2-one;

7-{2-[(5-Methoxy-1,2,3,4-tetrahydro-naphthalen-1-ylmethyl)-methyl-amino]-ethyl}-thiochroman-2-one;

6-{2-[(5-Methoxy-1,2,3,4-tetrahydro-naphthalen-1-ylmethyl)-methyl-amino]-ethyl}-thiochroman-2-one;

7-{2-[(5-Methoxy-1,2,3,4-tetrahydro-naphthalen-1-ylmethyl)-methyl-amino]-ethyl}-1H-quinolin-2-one;

6-{2-[(5-Methoxy-1,2,3,4-tetrahydro-naphthalen-1-ylmethyl)-methyl-amino]-ethyl}-1H-quinolin-2-one;

7-{2-[(5-Methoxy-1,2,3,4-tetrahydro-naphthalen-1-ylmethyl)-methyl-amino]-ethyl}-chromene-2-one;

6-{2-[(5-Methoxy-1,2,3,4-tetrahydro-naphthalen-1-ylmethyl)-methyl-amino]-ethyl}-chromene-2-one;

7-{2-[(5-Methoxy-1,2,3,4-tetrahydro-naphthalen-1-ylmethyl)-methyl-amino]-ethyl}-thiochromene-2-one;

5-{2-[(5-Methoxy-1,2,3,4-tetrahydro-naphthalen-1-ylmethyl)-methyl-amino]-ethyl}-benzo[1,3]dioxol-2-one;

5-{2-[(5-Methoxy-1,2,3,4-tetrahydro-naphthalen-1-ylmethyl)-methyl-amino]-ethyl}-3H-benzoxazol-2-one;

5-{2-[(5-Methoxy-1,2,3,4-tetrahydro-naphthalen-1-ylmethyl)-methyl-amino]-ethyl}-benzo[1,3]oxathiol-2-one;

5-{2-[(5-Methoxy-1,2,3,4-tetrahydro-naphthalen-1-ylmethyl)-methyl-amino]-ethyl}-3H-benzothiazol-2-one;

5-{2-[(5-Methoxy-1,2,3,4-tetrahydro-naphthalen-1-ylmethyl)-methyl-amino]-ethyl}-benzo[1,3]dithiol-2-one;

5-{2-[(5-Methoxy-1,2,3,4-tetrahydro-naphthalen-1-ylmethyl)-methyl-amino]-ethyl}-1,3-dihydro-benzimidazol-2-one;

N-[2-(2H-Benzotriazol-5-yl)-ethyl]-N-(5-methoxy-1,2,3,4-tetrahydro-naphthalen-1-ylmethyl)-N-methylamine;

N-{2-(Benzo[1,2,5]oxadiazol-5-yl)-ethyl}-N-(5-methoxy-1,2,3,4-tetrahydro-naphthalen-1-ylmethyl)-N-methylamine;

N-{2-(Benzo[1,2,5]thiadiazol-5-yl)-ethyl}-N-(5-methoxy-1,2,3,4-tetrahydro-naphthalen-1-ylmethyl)-N-methylamine;

N-{2-(Benzo[1,2,3]thiadiazol-5-yl)-ethyl}-N-(5-methoxy-1,2,3,4-tetrahydro-naphthalen-1-ylmethyl)-N-methylamine;

N-{2-(Benzo[1,2,3]oxadiazol-5-yl)-ethyl}-N-(5-methoxy-1,2,3,4-tetrahydro-naphthalen-1-ylmethyl)-N-methylamine;

N-{2-(1H-Benzotriazol-5-yl)-ethyl}-N-(5-methoxy-1,2,3,4-tetrahydro-naphthalen-1-ylmethyl)-N-methylamine;

6-{2-[(5-Methoxy-1,2,3,4-tetrahydro-naphthalen-1-ylmethyl)-methyl-amino]-ethyl}-thiochromene-2-one;

7-{2-[(5-Methoxy-1,2,3,4-tetrahydro-naphthalen-1-ylmethyl)-methyl-amino]-ethyl}-1,4-dihydro-2H-quinolin-3-one;

6-{2-[(5-Methoxy-1,2,3,4-tetrahydro-naphthalen-1-ylmethyl)-methyl-amino]-ethyl}-1,4-dihydro-2H-quinolin-3-one;

7-{2-[(5-Methoxy-1,2,3,4-tetrahydro-naphthalen-1-ylmethyl)-methyl-amino]-ethyl}-chroman-3-one;

6-{2-[(5-Methoxy-1,2,3,4-tetrahydro-naphthalen-1-ylmethyl)-methyl-amino]-ethyl}-chroman-3-one;

7-{2-[(5-Methoxy-1,2,3,4-tetrahydro-naphthalen-1-ylmethyl)-methyl-amino]-ethyl}-thiochroman-3-one;

6-{2-[(5-Methoxy-1,2,3,4-tetrahydro-naphthalen-1-ylmethyl)-methyl-amino]-ethyl}-thiochroman-3-one;

7-{2-[(5-Methoxy-1,2,3,4-tetrahydro-naphthalen-1-ylmethyl)-methyl-amino]-ethyl}-3,4-dihydro-2H-naphthalen-1-one;

6-{2-[(5-Methoxy-1,2,3,4-tetrahydro-naphthalen-1-ylmethyl)-methyl-amino]-ethyl}-3,4-dihydro-2H-naphthalen-1-one;

7-{2-[(5-Methoxy-1,2,3,4-tetrahydro-naphthalen-1-ylmethyl)-methyl-amino]-ethyl}-2,3-dihydro-1H-quinolin-4-one;

6-{2-[(5-Methoxy-1,2,3,4-tetrahydro-naphthalen-1-ylmethyl)-methyl-amino]-ethyl}-2,3-dihydro-1H-quinolin-4-one;

7-{2-[(5-Methoxy-1,2,3,4-tetrahydro-naphthalen-1-ylmethyl)-methyl-amino]-ethyl}-chroman-4-one;

6-{2-[(5-Methoxy-1,2,3,4-tetrahydro-naphthalen-1-ylmethyl)-methyl-amino]-ethyl}-chroman-4-one;

7-{2-[(5-Methoxy-1,2,3,4-tetrahydro-naphthalen-1-ylmethyl)-methyl-amino]-ethyl}-thiohroman-4-one;

6-{2-[(5-Methoxy-1,2,3,4-tetrahydro-naphthalen-1-ylmethyl)-methyl-amino]-ethyl}-thiochroman-4-one;

7-{2-[(5-Methoxy-1,2,3,4-tetrahydro-naphthalen-1-ylmethyl)-methyl-amino]-ethyl}-1H-quinolin-4-one;

6-{2-[(5-Methoxy-1,2,3,4-tetrahydro-naphthalen-1-ylmethyl)-methyl-amino]-ethyl}-1H-quinolin-4-one;

7-{2-[(5-Methoxy-1,2,3,4-tetrahydro-naphthalen-1-ylmethyl)-methyl-amino]-ethyl}-chromen-4-one;

6-{2-[(5-Methoxy-1,2,3,4-tetrahydro-naphthalen-1-ylmethyl)-methyl-amino]-ethyl}-chromen-4-one;

7-{2-[(5-Methoxy-1,2,3,4-tetrahydro-naphthalen-1-ylmethyl)-methyl-amino]-ethyl}-thiochromen-4-one;

6-{2-[(5-Methoxy-1,2,3,4-tetrahydro-naphthalen-1-ylmethyl)-methyl-amino]-ethyl}-thiochromen-4-one;

7-{2-[(5-Methoxy-1,2,3,4-tetrahydro-naphthalen-1-ylmethyl)-methyl-amino]-ethyl}-1,4-dihydro-2H-isoquinolin-3-one;

7-{2-[(5-Methoxy-1,2,3,4-tetrahydro-naphthalen-1-ylmethyl)-methyl-amino]-ethyl}-isochroman-3-one;

7-{2-[(5-Methoxy-1,2,3,4-tetrahydro-naphthalen-1-ylmethyl)-methyl-amino]-ethyl}-isothiochroman-3-one;

7-{2-[(5-Methoxy-1,2,3,4-tetrahydro-naphthalen-1-ylmethyl)-methyl-amino]-ethyl}-isochroman-4-one;

6-{2-[(5-Methoxy-1,2,3,4-tetrahydro-naphthalen-1-ylmethyl)-methyl-amino]-ethyl}-isochroman-4-one;

7-{2-[(5-Methoxy-1,2,3,4-tetrahydro-naphthalen-1-ylmethyl)-methyl-amino]-ethyl}-2,3-dihydro-1H-isoquinolin-4-one;

6-{2-[(5-Methoxy-1,2,3,4-tetrahydro-naphthalen-1-ylmethyl)-methyl-amino]-ethyl}-2,3-dihydro-1H-isoquinolin-4-one;

6-{2-[(5-Methoxy-1,2,3,4-tetrahydro-naphthalen-1-ylmethyl)-methyl-amino]-ethyl}-3,4-dihydro-2H-isoquinolin-1-one;

6-{2-[(5-Methoxy-1,2,3,4-tetrahydro-naphthalen-1-ylmethyl)-methyl-amino]-ethyl}-3,4-dihydro-2H-isochroman-1-one;

6-{2-[(5-Methoxy-1,2,3,4-tetrahydro-naphthalen-1-ylmethyl)-methyl-amino]-ethyl}-3,4-dihydro-2H-isothiochroman-1-one;

6-{2-[(5-Methoxy-1,2,3,4-tetrahydro-naphthalen-1-ylmethyl)-methyl-amino]-ethyl}-3,4-dihydro-2H-isothiochromen-1-one;

6-{2-[(5-Methoxy-1,2,3,4-tetrahydro-naphthalen-1-ylmethyl)-methyl-amino]-ethyl}-isochromen-1-one;

6-{2-[(5-Methoxy-1,2,3,4-tetrahydro-naphthalen-1-ylmethyl)-methyl-amino]-ethyl}-2H-isoquinolin-1-one;

6-{2-[(5-Methoxy-1,2,3,4-tetrahydro-naphthalen-1-ylmethyl)-methyl-amino]-ethyl}-4H-isoquinolin-3-one;

6-{2-[(5-Methoxy-1,2,3,4-tetrahydro-naphthalen-1-ylmethyl)-methyl-amino]-ethyl}-3,4-dihydro-2H-phthalazin-1-one;

7-{2-[(5-Methoxy-1,2,3,4-tetrahydro-naphthalen-1-ylmethyl)-methyl-amino]-ethyl}-1H-benzo[d][1,2]oxazin-4-one;

7-{2-[(5-Methoxy-1,2,3,4-tetrahydro-naphthalen-1-ylmethyl)-methyl-amino]-ethyl}-1H-benzo[d][1,2]thiazin-4-one;

6-{2-[(5-Methoxy-1,2,3,4-tetrahydro-naphthalen-1-ylmethyl)-methyl-amino]-ethyl}-4H-benzo[d][1,2]oxathiin-1-one;

6-{2-[(5-Methoxy-1,2,3,4-tetrahydro-naphthalen-1-ylmethyl)-methyl-amino]-ethyl}-3,4-dihydro-benzo[d][1,2]oxazin-1-one;

7-{2-[(5-Methoxy-1,2,3,4-tetrahydro-naphthalen-1-ylmethyl)-methyl-amino]-ethyl}-benzo[1,3]dioxin-4-one;

7-{2-[(5-Methoxy-1,2,3,4-tetrahydro-naphthalen-1-ylmethyl)-methyl-amino]-ethyl}-1,2-dihydro-benzo[d][1,3]oxazin-4-one;

7-{2-[(5-Methoxy-1,2,3,4-tetrahydro-naphthalen-1-ylmethyl)-methyl-amino]-ethyl}-benzo[d][1,3]oxazinin-4-one;

7-{2-[(5-Methoxy-1,2,3,4-tetrahydro-naphthalen-1-ylmethyl)-methyl-amino]-ethyl}-benzo[d][1,3]oxathiin-4-one;

6-{2-[(5-Methoxy-1,2,3,4-tetrahydro-naphthalen-1-ylmethyl)-methyl-amino]-ethyl}-benzo[d][1,3]oxathiin-4-one;

7-{2-[(5-Methoxy-1,2,3,4-tetrahydro-naphthalen-1-ylmethyl)-methyl-amino]-ethyl}-2,3-dihydro-benzo[e][1,3]thiazin-4-one;

7-{2-[(5-Methoxy-1,2,3,4-tetrahydro-naphthalen-1-ylmethyl)-methyl-amino]-ethyl}-benzo[e][1,3]thiazin-4-one;

7-{2-[(5-Methoxy-1,2,3,4-tetrahydro-naphthalen-1-ylmethyl)-methyl-amino]-ethyl}-2,3-dihydro-1H-quinazolin-4-one;

7-{2-[(5-Methoxy-1,2,3,4-tetrahydro-naphthalen-1-ylmethyl)-methyl-amino]-ethyl}-3H-quinazolin-4-one;

7-{2-[(5-Methoxy-1,2,3,4-tetrahydro-naphthalen-1-ylmethyl)-methyl-amino]-ethyl}-benzo[d][1,3]thiazin-4-one;

7-{2-[(5-Methoxy-1,2,3,4-tetrahydro-naphthalen-1-ylmethyl)-methyl-amino]-ethyl}-1,2-dihydro-benzo[d][1,3]thiazin-4-one;

7-{2-[(5-Methoxy-1,2,3,4-tetrahydro-naphthalen-1-ylmethyl)-methyl-amino]-ethyl}-benzo[d][1,3]oxathiin-4-one;

7-{2-[(5-Methoxy-1,2,3,4-tetrahydro-naphthalen-1-ylmethyl)-methyl-amino]-ethyl}-benzo[1,3]dithiin-4-one;

6-{2-[(5-Methoxy-1,2,3,4-tetrahydro-naphthalen-1-ylmethyl)-methyl-amino]-ethyl}-benzo[1,4]dithiin-2-one;

6-{2-[(5-Methoxy-1,2,3,4-tetrahydro-naphthalen-1-ylmethyl)-methyl-amino]-ethyl}-benzo[1,4]oxathiin-2-one;

6-{2-[(5-Methoxy-1,2,3,4-tetrahydro-naphthalen-1-ylmethyl)-methyl-amino]-ethyl}-4H-benzo[1,4]thiazin-3-one;

6-{2-[(5-Methoxy-1,2,3,4-tetrahydro-naphthalen-1-ylmethyl)-methyl-amino]-ethyl}-3,4-dihydro-1H-quinoxalin-2-one;

6-{2-[(5-Methoxy-1,2,3,4-tetrahydro-naphthalen-1-ylmethyl)-methyl-amino]-ethyl}-3,4-dihydro-benzo[1,4]oxazin-2-one;

6-{2-[(5-Methoxy-1,2,3,4-tetrahydro-naphthalen-1-ylmethyl)-methyl-amino]-ethyl}-3,4-dihydro-benzo[1,4]thiazin-2-one;

6-{2-[(5-Methoxy-1,2,3,4-tetrahydro-naphthalen-1-ylmethyl)-methyl-amino]-ethyl}-benzo[1,4]thiazin-2-one;

6-{2-[(5-Methoxy-1,2,3,4-tetrahydro-naphthalen-1-ylmethyl)-methyl-amino]-ethyl}-benzo[1,4]oxazin-2-one;

6-{2-[(5-Methoxy-1,2,3,4-tetrahydro-naphthalen-1-ylmethyl)-methyl-amino]-ethyl}-1H-quinoxalin-2-one;

6-{2-[(5-Methoxy-1,2,3,4-tetrahydro-naphthalen-1-ylmethyl)-methyl-amino]-ethyl}-4H-benzo[1,4]oxazin-3-one;

7-{2-[(5-Methoxy-1,2,3,4-tetrahydro-naphthalen-1-ylmethyl)-methyl-amino]-ethyl}-benzo[1,4]oxathiin-3-one;

6-{2-[(5-Methoxy-1,2,3,4-tetrahydro-naphthalen-1-ylmethyl)-methyl-amino]-ethyl}-4H-benzo[1,3]dithiin-2-one;

6-{2-[(5-Methoxy-1,2,3,4-tetrahydro-naphthalen-1-ylmethyl)-methyl-amino]-ethyl}-4H-benzo[d][1,3]oxathiin-2-one;

6-{2-[(5-Methoxy-1,2,3,4-tetrahydro-naphthalen-1-ylmethyl)-methyl-amino]-ethyl}-3,4-dihydro-benzo[e][1,3]thiazin-2-one;

6-{2-[(5-Methoxy-1,2,3,4-tetrahydro-naphthalen-1-ylmethyl)-methyl-amino]-ethyl}-benzo[e][1,3]thiazin-2-one;

6-{2-[(5-Methoxy-1,2,3,4-tetrahydro-naphthalen-1-ylmethyl)-methyl-amino]-ethyl}-1H-quinazolin-2-one;

6-{2-[(5-Methoxy-1,2,3,4-tetrahydro-naphthalen-1-ylmethyl)-methyl-amino]-ethyl}-benzo[e][1,3]oxazin-2-one;

6-{2-[(5-Methoxy-1,2,3,4-tetrahydro-naphthalen-1-ylmethyl)-methyl-amino]-ethyl}-3,4-dihydro-1H-quinazolin-2-one;

6-{2-[(5-Methoxy-1,2,3,4-tetrahydro-naphthalen-1-ylmethyl)-methyl-amino]-ethyl}-3,4-dihydro-benzo[e][1,3]oxazin-2-one;

6-{2-[(5-Methoxy-1,2,3,4-tetrahydro-naphthalen-1-ylmethyl)-methyl-amino]-ethyl}-4H-benzo[1,3]dioxin-2-one;

6-{2-[(5-Methoxy-1,2,3,4-tetrahydro-naphthalen-1-ylmethyl)-methyl-amino]-ethyl}-4H-benzo[d][1,3]oxathiin-2-one;

7-{2-[(5-Methoxy-1,2,3,4-tetrahydro-naphthalen-1-ylmethyl)-methyl-amino]-ethyl}-1,4-dihydro-benzo[c][1,2]thiazin-3-one;

7-{2-[(5-Methoxy-1,2,3,4-tetrahydro-naphthalen-1-ylmethyl)-methyl-amino]-ethyl}-1,4-dihydro-benzo[c][1,2]oxazin-3-one;

7-{2-[(5-Methoxy-1,2,3,4-tetrahydro-naphthalen-1-ylmethyl)-methyl-amino]-ethyl}-1,4-dihydro-2H-cinnolin-3-one;

7-{2-[(5-Methoxy-1,2,3,4-tetrahydro-naphthalen-1-ylmethyl)-methyl-amino]-ethyl}-4H-benzo[e][1,2]oxazin-3-one;

6-{2-[(5-Methoxy-1,2,3,4-tetrahydro-naphthalen-1-ylmethyl)-methyl-amino]-ethyl}-4H-benzo[e][1,2]oxazin-3-one;

7-{2-[(5-Methoxy-1,2,3,4-tetrahydro-naphthalen-1-ylmethyl)-methyl-amino]-ethyl}-1H-isoquinoline-4-one;

7-{2-[(5-Methoxy-1,2,3,4-tetrahydro-naphthalen-1-ylmethyl)-methyl-amino]-ethyl}-benzo[d][1,2]oxazin-1-one;

6-{2-[(5-Methoxy-1,2,3,4-tetrahydro-naphthalen-1-ylmethyl)-methyl-amino]-ethyl}-2H-phthalazin-1-one;

6-{2-[(5-Methoxy-1,2,3,4-tetrahydro-naphthalen-1-ylmethyl)-methyl-amino]-ethyl}-benzo[d][1,2]thiazin-1-one;

7-{2-[(5-Methoxy-1,2,3,4-tetrahydro-naphthalen-1-ylmethyl)-methyl-amino]-ethyl}-benzo[d][1,3]thiazin-4-one;

7-{2-[(5-Methoxy-1,2,3,4-tetrahydro-naphthalen-1-ylmethyl)-methyl-amino]-ethyl}-benzo[d][1,3]oxazin-4-one;

7-{2-[(5-Methoxy-1,2,3,4-tetrahydro-naphthalen-1-ylmethyl)-methyl-amino]-ethyl}-3H-quinazolin-4-one;

7-{2-[(5-Methoxy-1,2,3,4-tetrahydro-naphthalen-1-ylmethyl)-methyl-amino]-ethyl}-3H-quinolin-4-one;

7-{2-[(5-Methoxy-1,2,3,4-tetrahydro-naphthalen-1-ylmethyl)-methyl-amino]-ethyl}-3H-cinnolin-4-one;

6-{2-[(5-Methoxy-1,2,3,4-tetrahydro-naphthalen-1-ylmethyl)-methyl-amino]-ethyl}-benzo[e][1,2]thiazin-2-one;

6-{2-[(5-Methoxy-1,2,3,4-tetrahydro-naphthalen-1-ylmethyl)-methyl-amino]-ethyl}-benzo[e][1,3]oxazin-2-one;

7-{2-[(5-Methoxy-1,2,3,4-tetrahydro-naphthalen-1-ylmethyl)-methyl-amino]-ethyl}-1H-quinazolin-2-one;

6-{2-[(5-Methoxy-1,2,3,4-tetrahydro-naphthalen-1-ylmethyl)-methyl-amino]-ethyl}-1H-quinoxalin-2-one;

6-{2-[(5-Methoxy-1,2,3,4-tetrahydro-naphthalen-1-ylmethyl)-methyl-amino]-ethyl}-benzo[1,4]thiazin-2-one;

6-{2-[(5-Methoxy-1,2,3,4-tetrahydro-naphthalen-1-ylmethyl)-methyl-amino]-ethyl}-benzo[1,4]oxazin-2-one;

7-{2-[(5-Methoxy-1,2,3,4-tetrahydro-naphthalen-1-ylmethyl)-methyl-amino]-ethyl}-4H-cinnolin-3-one;

7-{2-[(5-Methoxy-1,2,3,4-tetrahydro-naphthalen-1-ylmethyl)-methyl-amino]-ethyl}-4H-benzo[e][1,2]thiazin-3-one;

6-{2-[(5-Methoxy-1,2,3,4-tetrahydro-naphthalen-1-ylmethyl)-methyl-amino]-ethyl}-4H-phthalazin-1-one;

7-{2-[(5-Methoxy-1,2,3,4-tetrahydro-naphthalen-1-ylmethyl)-methyl-amino]-ethyl}-1H-cinnolin-4-one;

7-{2-[(5-Methoxy-1,2,3,4-tetrahydro-naphthalen-1-ylmethyl)-methyl-amino]-ethyl}-benzo[e][1,2]oxazin-4-one;

7-{2-[(5-Methoxy-1,2,3,4-tetrahydro-naphthalen-1-ylmethyl)-methyl-amino]-ethyl}-benzo[e][1,2]thiazin-4-one;

7-{2-[(5-Methoxy-1,2,3,4-tetrahydro-naphthalen-1-ylmethyl)-methyl-amino]-ethyl}-benzo[e][1,3]thiazin-4-one;

7-{2-[(5-Methoxy-1,2,3,4-tetrahydro-naphthalen-1-ylmethyl)-methyl-amino]-ethyl}-benzo[e][1,3]oxazin-4-one; and

7-{2-[(5-Methoxy-1,2,3,4-tetrahydro-naphthalen-1-ylmethyl)-methyl-amino]-ethyl}-1H-quinazolin-4-one.

Preferred compounds of the present invention include, but are not limited to, the following:

N-[2-(2,3-Dihydrobenzofuran-5-yl)ethyl]-N-[(R)-5-methoxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]-N-methylamine;

N-[2-(Benzofuran-5-yl)ethyl]-N-[5-methoxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]-N-methylamine;

N-[2-(2,3-Dihydrobenzofuran-5-yl)ethyl]-N-[(R)-5-methoxy-8-fluoro-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]-N-methylamine;

N-[2-(Benzofuran-6-yl)ethyl]-N-[(R)-5-methoxy-1,2,3,4-tetrahydro-naphthalen-1-ylmethyl]-N-methylamine;

N-[2-(2,3-Dihydrobenzofuran-5-yl)ethyl]-N-[(R)-5-ethoxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]-N-methylamine;

N-[2-(2,3-Dihydrobenzofuran-6-yl)ethyl]-N-[(R)-5-methoxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]-N-methylamine;

N-[2-(2,3-Dihydrobenzofuran-5-yl)ethyl]-N-[(R)-5,6-methylenedioxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]-N-methylamine;

N-[2-(2,3-Dihydrobenzo[b]thien-5-yl)ethyl]-N-[(R)-5-methoxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]-N-methylamine;

N-[2-(Benzimidazol-5-yl)ethyl]-N-[(R)-5-methoxy-1,2,3,4-tetrahydro-naphthalen-1-ylmethyl]-N-methylamine;

N-[2-(Benzoxazol-6-yl)ethyl]-N-[(R)-5-methoxy-1,2,3,4-tetrahydro-naphthalen-1-ylmethyl]-N-methylamine;

N-[2-(Benzoxazol-5-yl)ethyl]-N-[(R)-5-methoxy-1,2,3,4-tetrahydro-naphthalen-1-ylmethyl]-N-methylamine;

N-[2-(Benzoxazol-6-yl)ethyl]-N-[(R)-8-fluoro-5-methoxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]-N-methylamine;

N-[2-(Benzoxazol-5-yl)ethyl]-N-[(R)-8-fluoro-5-methoxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]-N-methylamine;

N-[2-([4H]-2,3-Dihydrobenzopyran-6-yl)ethyl]-N-[(R)-5-methoxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]-N-methylamine;

N-[2-(Indan-5-yl)ethyl]-N-[(R)-5-methoxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]-N-methylamine;

N-[2-(N-Methanesulfonamido-2,3-dihydroindol-5-yl)ethyl]-N-[(R)-5-methoxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]-N-methylamine;

N-[2-(Benzimidazol-5-yl)ethyl]-N-[(R)-8-fluoro-5-methoxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]-N-methylamine;

N-[2,3-Dihydroindol-5-yl)ethyl]-N-[(R)-5-methoxy-1,2,3,4-tetrahydro-naphthalen-1-ylmethyl]-N-methylamine,

N-[2-(2-Chlorobenzothiazol-6-yl)ethyl]-N-[(R)-5-methoxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]-N-methylamine;

N-[2-(Quinoxalin-6-yl)ethyl]-N-[(R)-5-methoxy-1,2,3,4-tetrahydro-naphthalen-1-ylmethyl]-N-methylamine;

N-[2-(Quinolin-6-yl)ethyl]-N-[(R)-5-methoxy-1,2,3,4-tetrahydro-naphthalen-1-ylmethyl]-N-methylamine;

N-[2-(Quinolin-7-yl)ethyl]-N-[(R)-5-methoxy-1,2,3,4-tetrahydro-naphthalen-1-ylmethyl]-N-methylamine;

N-[2-(Isoquinolin-6-yl)ethyl]-N-[(R)-5-methoxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]-N-methylamine;

N-[2-(Isoquinolin-7-yl)ethyl]-N-[(R)-5-methoxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]-N-methylamine;

N-[2-(N-Methanesulfonamido-2,3-dihydroindol-6-yl)ethyl]-N-[(R)-5-methoxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]-N-methylamine;

N-[2-(N-Propanesulfonamido-2,3-dihydroindol-6-yl)ethyl]-N-[(R)-5-methoxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]-N-methylamine;

N-[2-(N-Isobutanesulfonamido-2,3-dihydroindol-6-yl)ethyl]-N-[(R)-5-methoxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]-N-methylamine;

N-[2-(N-Methyl-2,3-dihydroindol-5-yl)ethyl]-N-[(R)-5-methoxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]-N-methylamine;

N-[2-(N-Methyl-2,3-dihydroindol-6-yl)ethyl]-N-[(R)-5-methoxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]-N-methylamine;

N-[2-(2,3-Dihydroindol-6-yl)ethyl]-N-[(R)-5-methoxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]-N-methylamine;

N-[2-(2,3-Dihydroindol-5-yl)ethyl]-N-[(R)-5-methoxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]-N-methylamine;

N-[2-(Indol-6-yl)ethyl]-N-[(R)-5-methoxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]-N-methylamine;

N-[2-(N-Methanesulfonamido-1,3-dihydroisoindol-5-yl)ethyl]-N-[(R)-5-methoxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]-N-methylamine;

N-[2-(N-Methyl-1,3-dihydroisoindol-5-yl)ethyl]-N-[(R)-5-methoxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]-N-methylamine;

N-[2-(1,3-Dihydroisoindol-5-yl)ethyl]-N-[(R)-5-methoxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]-N-methylamine;

N-[2-(Benzothiazol-6-yl)ethyl]-N-[(R)-5-methoxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]-N-methylamine;

N-[2-(2-Chlorobenzothiazol-5-yl)ethyl]-N-[(R)-5-methoxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]-N-methylamine;

N-[2-(Benzothiazol-5-yl)ethyl]-N-[(R)-5-methoxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]-N-methylamine;

N-[2-(Benzo[b]thien-5-yl)ethyl]-N-[(R)-5-methoxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]-N-methylamine;

N-[2-(2,3-Dihydro-benzo[b]thien-6-yl)ethyl]-N-[(R)-5-methoxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]-N-methylamine;

N-[2-(Benzo[b]en-6-yl)ethyl]-N-[(R)-5-methoxy-1,2,3,4-tetrahydro-naphthalen-1-ylmethyl]-N-methylamine;

N-[2-(1-Oxo-2,3-dihydrobenzo[b]thien-5-yl)ethyl]-N-[(R)-5-methoxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]-N-methylamine;

N-[2-(1,1-Dioxo-2,3-dihydrobenzo[b]thien-5-yl)ethyl]-N-[(R)-5-methoxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]-N-methylamine;

N-[2-(1-Oxo-2,3-dihydrobenzo[b]thien-6-yl)ethyl]-N-[(R)-5-methoxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]-N-methylamine;

N-[2-(1,1-Dioxo-2,3-dihydrobenzo[b]thien-6-yl)ethyl]-N-[(R)-5-methoxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]-N-methylamine;

N-[2-(1,3-Dihydro-isobenzofuran-5-yl)-ethyl]-N-{(R)-5-methoxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]-N-methylamine;

N-[2-(Benzo[1,3]oxathiol-5-yl)-ethyl]-N-{(R)-5-methoxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]-N-methylamine;

N-[2-(2-Amino-benzothiazol-5-yl)-ethyl]-N-{(R)-5-methoxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]-N-methylamine;

N-[(2-Benzofuran-5-yl)-ethyl]-N-{(R)-5-methoxy-1,2,3,4-tetrahydro-naphthalen-1-ylmethyl]-N-methylamine;

N-[2-(N-Methyl-2,3-dihydro-1H-indol-5-yl)-ethyl]-N-[(R)-5-methoxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]-N-methylamine;

5-{2-[(R)-5-Methoxy-1,2,3,4-tetrahydro-naphthalen-1-ylmethyl)methyl-amino]-ethyl}-1,3-dihydro-indol-2-one;

N-[2-(N-Trifluoromethanesulfonamido-1,3-dihydroisoindol-5-yl)ethyl]-N-[(R)-5-methoxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]-N-methylamine;

N-[2-(N-Ethanesulfonamido-1,3-dihydroisoindol-5-yl)ethyl]-N-[(R)-5-methoxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]-N-methylamine;

N-[2-(Benzofuran-7-yl)ethyl-N-[(R)-8-fluoro-5-methoxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]-N-methylamine;

N-[2-(Benzofuran-6-yl)ethyl-N-[(R)-8-fluoro-5-methoxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]-N-methylamine;

N-[2-(2,3-Dihydrobenzofuran-6-yl)ethyl-N-[(R)-5-hydroxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]-amine;

N-[2-(2-Indolinone-6-yl)ethyl-N-[(R)-5-methoxy-1,2,3,4-tetrahydro-naphthalen-1-ylmethyl]-N-methylamine;

N-[2-(N-Methanesulfonamido-1,3-dihydroisoindol-5-yl)ethyl-N-[(R)-5,6-methylenedioxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]-N-ethylamine;

N-[2-(2,3-Dihydrobenzofuran-6-yl)ethyl-N-[(R)-5,6-methylenedioxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]-N-ethylamine;

N-[2-(N-Methanesulfonamido-1,3-dihydroisoindol-5-yl)ethyl-N-[(R)-5-methoxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]-N-ethylamine;

N-[2-(N-Methanesulfonamido-1,3-dihydroisoindol-5-yl)ethyl-N-[(R)-8-fluoro-5-methoxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]-N-methylamine ;

N-[2-(N-Methanesulfonamido-1,3-dihydroisoindol-5-yl)ethyl-N-[(R)-5,6-methylenedioxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]-N-methylamine;

N-[2-(2,3-Dihydrobenzofuran-6-yl)ethyl]-N-[(R)-5-ethoxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]-N-methylamine;

N-[2-(2,3-Dihydrobenzofuran-7-yl)ethyl]-N-[(R)-5-methoxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]-N-methylamine;

N-[2-(Benzofuran-7-yl)ethyl]-N-[(R)-5-methoxy-1,2,3,4-tetrahydro-naphthalen-1-ylmethyl]-N-methylamine;

N-[2-(2,3-Dihydrobenzofuran-7-yl)ethyl]-N-[(R)-5,6-methylenedioxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]-N-methylamine;

N-[2-(N-Methanesulfonamido-1,3-dihydroisoindol-5-yl)ethyl]-N-[(R)-5-ethoxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]-N-methylamine;

N-[2-(Quinolin-5-yl)ethyl]-N-[(R)-5-methoxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]-N-methylamine;

N-[2-(Quinolin-8-yl)ethyl]-N-[(R)-5-methoxy-1,2,3,4-tetrahydro-naphthalen-1-ylmethyl]-N-methylamine;

N-[2-(Quinolin-6-yl)ethyl]-N-[(R)-5,6-methylenedioxy-1,2,3,4-tetrahydro-naphthalen-1-ylmethyl]-N-methylamine;

N-[2-(Benzo[b]thien-3-yl)ethyl]-N-[(R)-5-methoxy-1,2,3,4-tetrahydro-naphthalen-1-ylmethyl]-N-methylamine;

N-[2-(Benzo[b]thien-2-yl)ethyl]-N-[(R)-5-methoxy-1,2,3,4-tetrahydro-naphthalen-1-ylmethyl]-N-methylamine;

N-[2-(Indol-3-yl)ethyl]-N-[(R)-5-methoxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]-N-methylamine;

N-[2-(N-Trifluoromethanesulfonamido-2,3-dihydroindol-6-yl)ethyl]-N-[(R)-5-methoxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]-N-methylamine;

N-[2-(2,3-Dihydrobenzo[b]thien-5-yl)ethyl]-N-[(R)-5,6-methylenedioxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]-N-methylamine;

N-[2-(N-Methanesulfonamido-2,3-dihydroindol-6-yl)ethyl]-N-[(R)-5,6-methylenedioxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]-N-methylamine ;

N-[2-(2,3-Dihydroindol-5-yl)ethyl]-N-[(R)-5,6-methylenedioxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]-N-methylamine;

N-[2-(Benzofuran-5-yl)ethyl]-N-[(R)-5,6-methylenedioxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]-N-methylamine;

N-[2-(2,2-Dioxo-1,3-dihydrobenzo[c]thien-5-yl)ethyl]-N-[(R)-5-methoxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]-N-methylamine;

N-[2-(2,2-Dioxo-1,3-dihydrobenzo[c]thien-5-yl)ethyl]-N-[(R)-5,6-methylenedioxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]-N-methylamine;

N-[2-(Benzofuran-7-yl)ethyl]-N-[(R)-5,6-methylenedioxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]-N-methylamine;

N-[2-(1,1-Dioxo-2,3-dihydrobenzo[b]thien-5-yl)ethyl]-N-[(R)-5-methoxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]-N-methylamine;

N-[2-(3-Methyl-benzofuran-5-yl)ethyl]-N-[(R)-5-methoxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]-N-methylamine;

N-[2-(2-Methyl-benzofuran-5-yl)ethyl]-N-[(R)-5-methoxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]-N-methylamine;

N-[2-(2,3-Dihydrobenzo[b]thien-5-yl)ethyl]-N-[(R)-5-methoxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]-N-ethylamine;

N-[2-(Benzofuran-6-yl)ethyl]-N-[(R)-5-methoxy-1,2,3,4-tetrahydro-naphthalen-1-ylmethyl]-amine;

N-[3-(2-(1,2-Benzisothiazolin-3-one-1,1-dioxide))propyl]-N-[(R)-5-methoxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]-N-methylamine;

N-[3-(2-(1,2-benzisothiazolin-3-one-1,1-dioxide))ethyl]-N-[(R)-5-methoxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]-N-methylamine;

N-[2-(2,3-Dihydrobenzofuran-6-yl)ethyl]-N-[(R)-5,6-methylenedioxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]-N-methylamine;

N-[2-(2,3-Dihydrobenzo[b]thien-5-yl)ethyl]-N-[(R)-5-ethoxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]-N-methylamine;

5-{2-[((R)-5,6-Methylenedioxy-1,2,3,4-tetrahydro-naphthalen-1-ylmethyl)methyl-amino]-ethyl}-1,3-dihydro-indol-2-one;

N-[2-(2-Chloro-benzothiazol-6-yl)-ethyl]-N-{(R)-5,6-methylenedioxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]-N-methylamine;

N-[2-(Benzothiazol-6-yl)-ethyl]-N-{(R)-5,6-methylenedioxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]-N-methylamine;

N-[2-(N-Methanesulfonamido-1,3-dihydroisoindol-5-yl)ethyl]-N-[(R)-5,6-methylenedioxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]-N-methylamine;

6-{2-[((R)-5-,6-Methylenedioxy-1,2,3,4-tetrahydro-naphthalen-1-ylmethyl)methyl-amino]-ethyl}-3H-benzoxazol-2-one;

N-[2-(2-Amino-benzothiazol-6-yl)-ethyl]-N-{(R)-5,6-methylenedioxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]-N-methylamine;

N-[2-(Benzoxazol-6-yl)-ethyl]-N-{(R)-5,6-methylenedioxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]-N-methylamine;

N-[2-(Benzo[b]thien-5-yl)ethyl]-N-[(R)-5,6-Methylenedioxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]-N-methylamine;

N-[2-(Benzofuran-6-yl)ethyl]-N-[(R)-5,6-methylenedioxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]-N-methylamine;

N-[2-(2,3-Dihydrobenzofuran-4-yl)ethyl]-N-[(R)-5-methoxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]-N-methylamine;

N-[2-(2,3-Dihydrobenzofuran-4-yl)ethyl]-N-[(R)-5,6-methylenedioxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]-N-methylamine;

6-{2-[((R)-5-Methoxy-1,2,3,4-tetrahydro-naphthalen-1-ylmethyl)methyl-amino]-ethyl}-3H-benzoxazol-2-one;

5-{2-[((R)-5-Methoxy-1,2,3,4-tetrahydro-naphthalen-1-ylmethyl)methyl-amino]-ethyl}-3H-imidazol-2-one; and

5-{2-[((R)-5-Methoxy-1,2,3,4-tetrahydro-naphthalen-1-ylmethyl)methyl-amino]-ethyl}-3H-benzoxazol-2-one.

As used throughout this specification and the appended claims, the following terms have the meanings ascribed to them:

The term "lower alkyl" as used herein refers to straight or branched chain saturated hydrocarbon radicals having from one to six carbon atoms. Representative examples of lower alkyl groups include methyl, ethyl, *n*-propyl, *iso*-propyl, *n*-butyl, *sec*-butyl, *iso*-butyl, *tert*-butyl, and the like.

The term "lower alkoxy" as used herein refers to a lower alkyl group, as defined herein, which is bonded to the parent molecular moiety through an oxygen atom. Representative examples of lower alkoxy groups include methoxy, ethoxy, *tert*-butoxy, and the like.

The term "thioalkyloxy" as used herein refers to a lower alkyl group, as defined herein, which is bonded to the parent molecular moiety through a sulfur atom. Representative examples of thioalkyloxy groups include methylthio, ethylthio, isopropylthio, and the like.

The term "alkylamino" as used herein refers to one or two lower alkyl groups, as defined herein, which are bonded to the parent molecular moiety through a nitrogen atom. Representative examples of alkylamino groups include methylamino, dimethylamino, ethylamino, diethylamino, isopropylamino, and the like.

The term "alkylsulfonyl" as used herein refers to a lower alkyl group bonded to the parent molecular moiety through a sulfonyl ($-SO_2-$) group. Representative examples of alkylsulfonyl groups include methanesulfonyl, ethanesulfonyl, isopropylsulfonyl, and the like.

The term "alkylsulfonylamino" as used herein refers to a lower alkyl group bonded to the parent molecular moiety through a sulfonylamino ($-SO_2NR-$) group in which R can be hydrogen or lower alkyl. Representative examples of alkylsulfonylamino groups include methanesulfonamido, ethanesulfonamido, N-methyl-methanesulfonamido, and the like.

The term "halo" or "halogen" as used herein means fluorine, iodine, bromine, or chlorine.

The term "methylenedioxy" or "ethylenedioxy" as used herein refers to either a methylene group, $-CH_2-$, or an ethylene group, $-CH_2CH_2-$, attached to the parent molecular moiety through oxygen atoms to form either five or six membered rings.

The term "substituted phenyl" as used herein refers to a phenyl ring with one, two, or three substituents independently selected from lower alkyl, halo, hydroxy, lower alkoxy, amino, and thioalkyloxy.

The term "pharmaceutically acceptable salts" refers to the pharmaceutically acceptable, relatively nontoxic, inorganic or organic acid addition salts of the compounds of the present invention. These salts can be prepared *in situ* during the final isolation and purification of the compounds, or by separately reacting the free base with a suitable organic or inorganic acid. Representative salts include the hydrochloride, hydrobromide, sulfate, phosphate, nitrate, bisulfate, acetate, oxalate, valerate, oleate, palmitate, methanesulfonate, stearate, laurate, borate, benzoate, lactate, phosphate, tolsylate, citrate, maleate, fumarate, succinate, tartrate, napsylate, and the like. Those compounds having more than one basic site can be isolated as bis-salts, for example, dihydrochloride, bis-methanesulfonate, and the like.

The standard chirality descriptors "R" and "S" are used to indicate an isomerically pure center, "RS" to indicate a mixture, and "R/S" to indicate a single pure isomer of undetermined configuration. The assignment of "R" and "S" depends on the priority ranking of atoms or groups attached to the asymmetric center

as determined by the Cahn-Ingold-Prelog Sequence Rule (International Union of Pure and Applied Chemistry, "Nomenclature of Organic Chemistry, Sections, A, B, C, D, E, F, and H", Pergamon Press, Oxford, **1979**; Cahn, R.S., Ingold, C.K., Prelog, V., *Angew. Chem., Int. Ed. Engl.* **1966**, *5*: 385; and Prelog, V., Helmchen, G., *Angew. Chem., Int. Ed. Engl.* **1982**, *21*: 567).

Biological Assay Methods

The compounds were assessed for alpha-adrenergic receptor subtype selectivity by use of radioligand binding techniques as described previously (DeBernardis *et al.*, *J. Med. Chem.*, **1985**, *28*: 1398). Affinity for the alpha-1 receptor was assessed using rat liver homogenates and the radioligand [^{3}H]-prazosin; whereas for the alpha-2 receptor, rat cerebral cortices and the radioligand [^{3}H]-rauwolscine were utilized. Results obtained from the binding studies are shown in Table 1 for a representative sample of compounds disclosed herein, showing clearly the excellent affinity for the alpha-2 receptor, as well as the high degree of selectivity relative to the alpha-1 adrenorecptor.

The primary method of evaluation of biogenic amine uptake activity has been the *in vitro* determination of the inhibition of radioactive amine uptake by synaptosome preparations of brain tissue. Basic procedures used are those described by Snyder and Coyle (Snyder, S.H. and J.T. Coyle, Regional Differences in ^{3}H-Norepinephrine and ^{3}H-Dopamine Uptake into Rat Brain Homogenates, *Journal of Pharmacology and Experimental Therapeutics* **1969**, *165*: 78-86) and Wong *et al.* (Wong, D.T., J-S. Horng and R.W. Fuller, Kinetics of Serotonin Accumulation into Synaptosomes of Rat Brain--Effects of Amphetamine and Chloroamphetamines, *Biochemical Pharmacology* **1973**, *22*: 311-322). Briefly, male Sprague-Dawley rats were decapitated and regions of their brains dissected according to the procedures of Glowinski and Iversen (Glowinski, J. and L.L. Iversen, Regional Studies of Catecholamines in the Rat Brain--I: The Disposition of [^{3}H]-Norepinephrine, [^{3}H]-Dopamine and [^{3}H]-DOPA in Various Regions of the Brain, *Journal of Neurochemistry* **1966**, *13*: 655-669). Hypothalamus (norepinephrine-), cortex (serotonin-) and striatum (dopamine-uptake) were homogenized in 10, 5, and 20 volumes, respectively, of 0.32 *M* sucrose using a Teflon/glass Potter-Elvehjem tissue grinder. Samples were centrifuged at 1000 x G for 10 minutes and the supernatants harvested and used in the assay. Aliquots of tissue (100 µL) were added to 750 µL of Kreb's solution (composition in *mM*; sodium chloride 118, potassium chloride 4.0, calcium chloride

1.13, potassium dihydrogen phosphate 1.12, magnesium sulfate 1.20, sodium bicarbonate 2.4, D-glucose 5.0, disodium ethylenediaminetetraacetic acid 1.5, ascorbic acid 1.0, and Pargyline, 12.5 *μM*, pH = 7.4, aerated with 95% oxygen, 5% carbon dioxide), 50 μL of test compound diluted in 0.3 *mM* ascorbic acid, and 100 μL [^{3}H]-amine, final concentration approximately 100 *nM*. Tissues were incubated for 4 minutes at 37 °C, followed by rapid vacuum filtration over Whatman GF/B filters and washed with 50 *mM* Tris-HCl (pH = 7.4). Nonspecific uptake was estimated in duplicate samples incubated at 0 °C. Data were analyzed as described previously (J.F. DeBernardis, D.J. Kerkman, D.L. Arendsen, S.A. Buckner, J.J. Kyncl, and A.A. Hancock, Conformationally Defined Adrenergic Agents. 5. Resolution, Absolute Configuration, and Pharmacological Characterization of the Enantiomers of 2-[5,6-Dihydroxy-1,2,3,4-tetrahydro-1-naphthyl]imidazoline: A Potent Agonist at α-Adrenoceptors, *Journal of Medicinal Chemistry* **1987**, *30*: 1011-1017).

Table 1

Example	α-1 (nM)	α-2 (nM)	NE (μM)	5-HT (μM)	DA (μM)
19	24	1.8	0.906	0.015	4.911
20	80	7.8	0.727	0.041	5.556
21	26	1.0	1.392	0.073	6.678
22	109	1.7	0.872	0.014	7.796
23	134	2.0	3.334	0.094	7.554
24	111	2.6	2.022	0.008	9.648
25	118	3.4	4.397	0.052	3.188
26	30	1.3	2.078	0.014	7.007
27	31	7.7	0.860	0.011	7.759
28	26	1.6	1.066	0.005	3.948
29	48	1.6	1.485	0.017	4.736
30	31	0.38	3.900	0.133	5.694
31	21	0.50	1.146	0.122	17.267
32	56	6.2	0.342	0.127	4.965
33	125	10	1.252	0.070	3.806
34	30	5	1.108	0.076	5.310
35	21	1.6	1.306	0.129	6.572
36	41	4	0.677	0.043	8.066

Table 1 (continued)

37	100	1.5	4.072	0.017	4.314
38	26	1.4	3.868	0.063	4.001
39	31	4	1.514	0.002	10.719
47	94	10	1.149	0.017	6.452
48	52	5	2.699	0.003	20.622
51	13	2.0	0.745	0.009	2.528
58	18	2	21.696	0.248	24.500
61	20	5	0.224	0.017	0.760
62	54	2	1.163	0.017	9.567
63	54	15	1.203	0.028	15.655
64	4.5	5	4.681	0.022	13.182
75	606.6	153.6	3.121	0.060	26.959
76	32.45	6.74	0.667	0.226	12.736
77	46.91	5.99	1.061	0.022	12.921
79	93.35	1.66	0.681	0.096	7.008
80	106.56	1.3	0.636	1.000	4.932
82	50.12	12	0.190	0.056	3.098
83	133.21	14.05			
84	331.68	10.66	0.864	0.024	15.783
85	162.71	4.6	1.470	0.139	12.796
86	108.36	5.22	0.591	0.085	10.710
87	42.96	6.07	1.800	0.209	31.950
89	428.05	5.54	5.109	0.165	6.941
90	63.2	4.02	1.461	0.022	13.376
91	75.8	2.8	1.000	0.019	2.026
92	64.24	1.67	5.937	0.010	15.887
93	371.77	10.72			
94	22.99	11.43	2.870	0.058	9.369
95	43.83	5.1	2.099	0.068	6.737
96	76.93	6.79			
97	169.56	8.83			
98	79.98	35.35			
100	16.74	17.19			
101	312.75	124.33	7.915	0.520	20.035

Table 1 (concluded)

102	132.69	5.21	1.993	0.016	5.732
103	241.87	9.42	3.730	0.101	20.641
104	79.29	9.06	1.483	0.238	16.580
105	213.26	16.46			
106	36.99	1.69			
107	216.4	2.26			
108	184.69	3.27	1.879	0.029	7.871
112	41.87	2.31	0.552	0.106	8.225
114	51.32	46.63	6.444	0.127	15.540
115	359.14	54.83	5.268	0.045	47.490
116	303.41	3.12	5.957	0.058	24.839
117	173.75	2.12	3.801	0.169	8.943
118	45.58	7.03			
119	588.6	20.46			
120	100.7	6.52			
122	59.82	6.79	3.610	0.029	12.968
123	79.2	10.06			
124	153.97	3.83	1.801	0.017	22.729
125	128.5	20.23	2.761	1.000	2.446
126	314.38	5.56	8.56	0.050	8.080
Rauwolscine	450	2.8	>100	>100	>100
Fluoxetine	>1000	>1000	1.307	0.300	15.193

The compounds of the invention can be administered in any effective pharmaceutically acceptable form to warm blooded animals, *e.g.*, in oral, parenteral or infusable dosage forms, or as a buccal or nasal spray. Suitable routes of administration include, for example, intramuscular, intravenous, intraperitoneal or subcutaneous administration of the compounds.

In addition to the active compounds, compositions according to this invention for parenteral injection may comprise pharmaceutically acceptable sterile aqueous or nonaqueous solutions, suspensions or emulsions. Examples of suitable nonaqueous carriers, diluents, solvents or vehicles include propylene glycol, polyethylene glycol, vegetable oils, such as olive oil, and injectable organic esters such as ethyl oleate. Such compositions may also contain adjuvants such as

preserving, wetting, emulsifying, and dispersing agents. They may be sterilized, for example, by filtration through a bateria-retaining filter, or by incorporating sterilizing agents into the compositions. They can also be manufactured in the form of sterile solid compositions which can be dissolved in sterile water, or other sterile injectable medium, immediately before use.

Solid dosage forms for oral admistration include capsules, tablets, pills, powders, and granules. In such solid dosage forms, the active compound may be admixed with at least one inert diluent such as sucrose, lactose, or starch. Such dosage forms may also comprise, as is normal practice, additional substances other than inert diluents, *e.g.*, lubricating agents such as magnesium stearate. In the case of capsules, tablets, and pills, the dosage forms may also comprise buffering agents. Tablets and pills can additionally be prepared with enteric coatings.

Liquid dosage forms for oral administration include pharmaceutically acceptable emulsions, solutions, suspensions, syrups, and elixirs containing inert diluents commonly used in the art, such as water. Besides such inert diluents, compositions may also comprise adjuvants, such as wetting agents, emulsifying and suspending agents, and sweetening, flavoring and perfuming agents.

Actual dosage levels of active ingredient in the compositions of the invention may be varied so as to obtain an amount of active ingredient effective to obtain a desired therapeutic response for a particular composition and method of administration. The selected dosage level therefore depends upon the activity of the particular compound, the desired therapuetic effect, the route of administration, the desired duration of treatment, the severity of the condition being treated, the condition and prior medical history of the patient being treated and other factors. However, it is within the skill of the art to start doses of the compound at levels lower than required to achieve the desired therapeutic effect and to gradually increase the dosage until the desired effect is achieved.

Generally, dosage levels of about 0.1 to 200 mg, more preferably about 0.5 to 150 mg and most preferably about 1 to 125 mg of active ingredient per kg of body weight per day are administered orally to a mammalian patient suffering from depression. If desired, the daily dose may be divided into multiple doses for administration, *e.g.*, two to four separate doses per day.

Synthesis of the Compounds of the Invention

In general, the compounds of the present invention can be prepared as illustrated in Scheme 1. For illustration purposes a 5-membered ring heterocycle is

used; the analogous reactions can be carried out on 6-membered ring heterocycles as well. According to this reaction scheme, the appropriate heterocyclic acetic acid 1 is reacted with oxalyl chloride or other appropriate chlorinating agent in methylene chloride containing dimethylformamide to give acid chloride 2. The appropriately substituted aminomethyl tetrahydronaphthalene 3, prepared by the procedure described in International Patent Application Number WO 89/06645, is reacted with the acid chloride using triethylamine in methylene chloride or other appropriate coupling conditions. The carboxamide 4 is reduced with diborane or other appropriate reducing agent and acidified to give the secondary amine salt 5. This salt can be reductively alkylated using formaldehyde and an appropriate reducing agent such as sodium borohydride or other alkylation procedures to give the tertiary amine 6.

Those heterocyclic acetic acids 1 which are not commercially available are obtained by synthesis. Some general methods for preparing these intermediates are shown in Scheme 2. One general method is described in Scheme 2A, where Z can be >O, >S, or >NH. Friedel Crafts acylation of 7 yields the acylated intermediate 8. Rearrangement of 8 to the phenylacetic acid side chain 1a can be effected by one of a variety of methods including Willgerodt-Kindler reaction or thallium-mediated oxidative rearrangement (Ref.: *J. Am. Chem. Soc.* **1971**, *93*, 4919). The acid fragment 1a can be further elaborated by the procedures described in Scheme 1. Alternatively, the side chain acid portion may be dehydrogenated to yield yet another heterocyclic fragment 1b for coupling and reduction to yield another final product.

The corresponding 6-yl compounds can be prepared as described in Scheme 2B, where X can be >O or >S. Alkylation of commercially available 9 with bromoacetaldehyde diethyl acetal affords 10. Dehydrative cyclization of 10 affords a heterocyclic intermediate 1c which can either be further elaborated by the procedures described in Scheme 1 or be hydrogenated or otherwise reduced to yield yet another heterocyclic fragment 1d for coupling and reduction.

Yet another heterocyclic substitution pattern is available by the method described in Scheme 2C. Allylic bis-halogenation of the commercially available 3,4-dimethyl intermedate 11, followed by displacement by an oxygen, sulfur, or nitrogen nucleophile yields either the cyclized intermedate 13 (when X = RNH_2 or NH_3), or a bis-substituted intermedate which can subsequently be cyclized (when X = >O, >S). The benzoic acid fragment 13 is readily elaborated via standard methods to the acetic acid side chain fragment 1e.

In cases where a methyl substituted heterocyclic fragment 14 is more readily accessible, elaboration is possible as shown in Scheme 2D. Allylic halogenation to give 15, followed by cyanide ion displacement to give 16 and then hydrolysis produces the desired heterocycle 1f.

Variously substituted quinoline containing side chains are prepared by standard literature methods; reaction of the appropriately substituted aniline derivative 17 with glycerol under acidic conditions gives 1g as shown in Scheme 2E. Catalytic hydrogenation of 1g affords the tetrahydroquinoline.

Approaches to the preparation of other six-membered nitrogen containing heterocycles are shown in Scheme 2F. Condensation of the appropriately substituted 1,2-dianiline 18 with 2,3-dihydroxy-1,4-dioxane yields the desired heterocycle 1h.

Appropriately substitued anilines 19 can serve as starting materials for the preparation of variously substituted benzothiazole derivatives as shown in Scheme 2G. Reaction of the aniline 19 with ammonium thiocyanate and bromine yields the 2-amino-benzothiazole 20, which can then be converted into a variety of 2-substituted benzothiazoles 1i (X = Cl, Br, CN, I, H, *etc.*).

In certain cases functional groups present on the heterocyclic portion of the molecule are incompatible with amine to acid coupling and/or amide reduction reaction conditions. An alternative approach for certain of these cases is shown in Scheme 2H. The requisite alkyl halides 23 (X = >O or >NH) are prepared via Friedel-Crafts acylation of 21 with chloroacetyl chloride to give chloroketone 22, followed by triethyl silane reduction. The further elaboration of compound 23 is shown in Scheme 3.

Appropriately substituted hydroxy phenylacetic acid esters 24 can serve as starting materials for the preparation of variously substituted isoxazoles, coumarins, dihydrocoumarins, and chromanones, as outlined in Scheme 2I. Formylation of the phenol by any of a variety of reagents (for example, hexamethylenetetramine and TFA, $POCl_3$ and DMF, $Zn(CN)_2$, *etc.*) provides a useful intermediate 25 for conversion into isoxazoles 26 using hydroxylamine-O-sulfonic acid and coumarins 27 using malonic acid condensation. The coumarin may be reduced using catalytic hydrogenation with a palladium catalyst to give the dihydro coumarin 28. Alternatively, the phenol 24 can be reacted with 3-bromopropanoic acid to give 29 and subsequently cyclized under acid catalysis to yield various 4-chromanones 30. The esters 26, 27, 28, and 30 can be hydrolyzed to give the carboxylic acids 1.

In yet another modification, appropriately substituted hydroxy phenylacetic acid esters 24 can serve as starting materials for the preparation of additional oxygen containing five membered ring heterocycles. Scheme 2J outlines the preparation of various benzofuranaones. The appropriate phenol 24 can be treated with chloroacetyl chloride in the presence of a Lewis acid to give the chloroacetyl derivative 31 followed by intramolecular cyclization in the presence of base to yield various benzofuran-3-ones 32. Alternatively, the phenol can be esterified with chloroacetic anhydride to give the chloroacetoxy derivative 33 followed by intramolecular Friedel Crafts alkylation to yield variously substituted benzofuran-2-ones 34. Esters 32 and 34 can be hydrolyzed to give the carboxylic acids 1.

Alternatively, appropriately substituted hydroxy phenylacetic acid esters 24 can serve as starting materials for the preparation of substituted oxathioles, as outlined in Scheme 2K. Reaction of 24 with thiocyanogen choride followed by base promoted cyclization yields the oxathiolone 35, which can also be converted to the oxathiole 36 via aqueous hydrochloric acid hydrolysis followed by treatment with dibromomethane in the presence of base. Esters 35 and 36 can be hydrolyzed to give the carboxylic acids 1.

Scheme 2L illustrates the preparation of variously substituted isoquinolines and tetrahydroisoquinolines. Isoquinolines 38 can be prepared by a variety of standard methods (such as Pomeranz-Fritsch reaction or various newer modifications, i.e. Hendrickson and Rodriqwuez, *J. Org. Chem.*, *48*, 3344 (1983)) from the methyl benzaldehyde 37. The methyl substituted isoquinoline 38 can be oxidized to the carboxylic acid 39, and then homologated via Arndt-Eistert synthesis to the desired isoquinoline-acetic acid 1j. These isoquinolines can be further elaborated to give tetahydroisoquinolines 1k by catalytic hydrogenation.

Scheme 2M illustrates the preparation of variously substituted quinazolines 1l. These compounds can be prepared from appropriately substituted anthranilic acids 40. Condensation with formamide yields the hydroxyquinazoline 41, which can then converted to the chloroquinazoline 42 using phosphorous oxychloride, which then is dechlorinated under a variety of conditions, including hydrogenolysis, to give 43. Further elaboration under standard conditions, for example, Arndt-Eistert reaction, yields the acetic acid side chain derivative 1l.

The known 5-nitro-isoindol-1,3-dione 44a (X = CO) and 5-nitrosaccharin 44b (X = SO_2) serve as starting materials for the preparation of various substituted phthalimide and saccharin side chains (Scheme 2N). Hydrogenation to give the amine, followed by diazotization and treatment with CuCN yields the desired cyano

derivative 45. Hydrolysis affords the carboxylic acid 46 and then Arndt-Eistert homologation yields the desired phthalimido- and saccharin-acetic acid derivates 1m. These derivatives can then be alkylated to yield various 2-alkyl phthalimide and saccharin derivatives 1n.

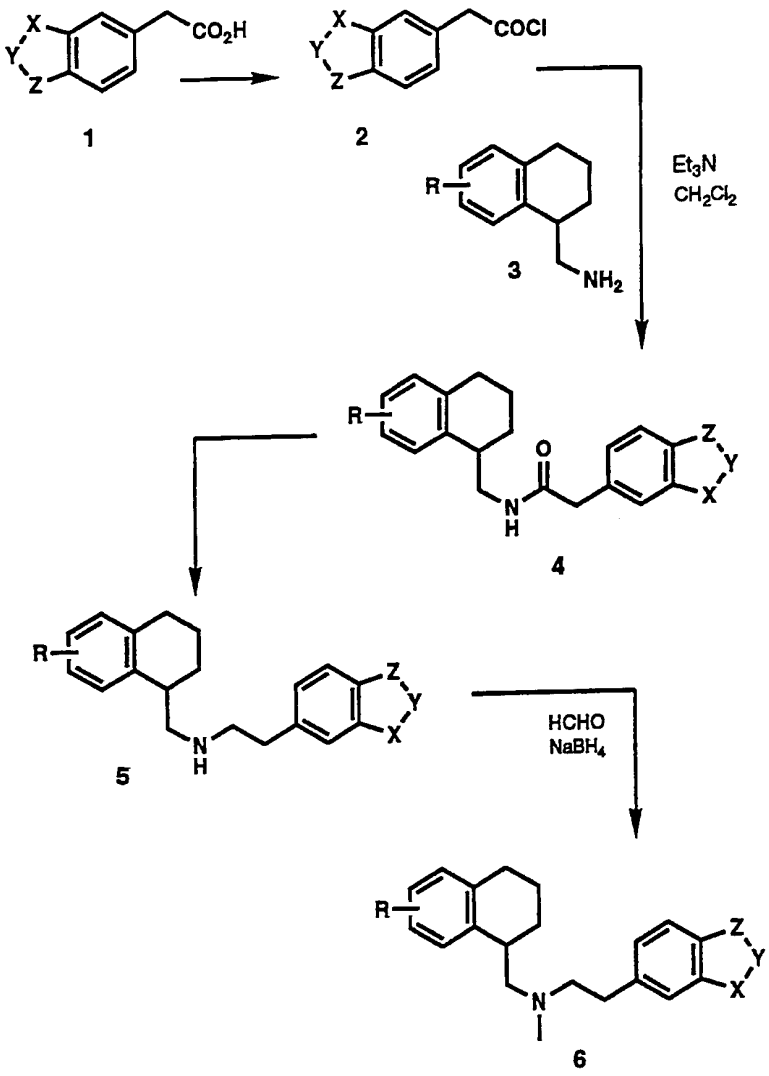
The heterocyclic chloroethyl side chain 23, described in Scheme 2H, is attached to the amine portion of the molecule 3 via an alkylation reaction as shown in Scheme 3, as opposed to the acetylation reaction shown in Scheme 1. Alkylation of the secondary amine 5 affords the tertiary amine 6b.

When the desired heterocyclic ring is not stable to the conditions required for coupling to the amine portion of the final product and/or reduction of the resultant carboxamide, it is expedient to synthesize the appended heterocyclic ring as the last step in the preparation of said compounds. Scheme 4 illustrates a generalized method, where X can be >O or >NH. The appropriately substituted nitro phenyl acetic acid 47 is coupled the N-alkylated amine portion of the molecule to give amide 48. Reduction of the carbonyl and nitro groups using catalytic hydrogenation followed by diborane reduction affords compound 49. Reaction of the amino-phenol (X = >O) or diamine (X = >NH) with various carboxylic acid ortho esters (such as triethyl orthoformate or triethyl orthoacetate) yields the desired benzoxazole (X = >O) or benzimidazole (X = >NH) final products 6c.

The preparation of the R-diastereomer of the 1,2,3,4-tetrahydronaphthalene is shown in Scheme 5. The commercially available 5-methoxy tetralone 50 is reacted with diethylcyanophosphonate (DECNP) in the presence of catalytic amounts of lithium cyanide. The intermediate addition product is treated with *p*-toluenesulfonic acid in toluene and then reduced with sodium borohydride in ethanol. Hydrolysis with potassium hydroxide in ethylene glycol gives the racemic carboxylic acid 51. Treatment of 51 with oxalyl chloride followed by dimethylethylamine affords the intermediate ketene 52 which when reacted with (R)-(-)-pantolactone in toluene at -70 °C affords the chiral ester 53. Reduction of 53 with lithium aluminum hydride in tetrahydrofuran affords the (R)-alcohol 54. Treatment of 54 with methanesulfonyl chloride affords the methanesulfonate 55. Treatment with sodium azide in dimethylformamide affords azide 56. Reduction of the azide with lithium aluminum hydride affords the (R)-primary amine 57. Reductive alkylation using ethyl formate followed by borane reduction affords the (R)-N-methyl compound 58.

40

SCHEME 1



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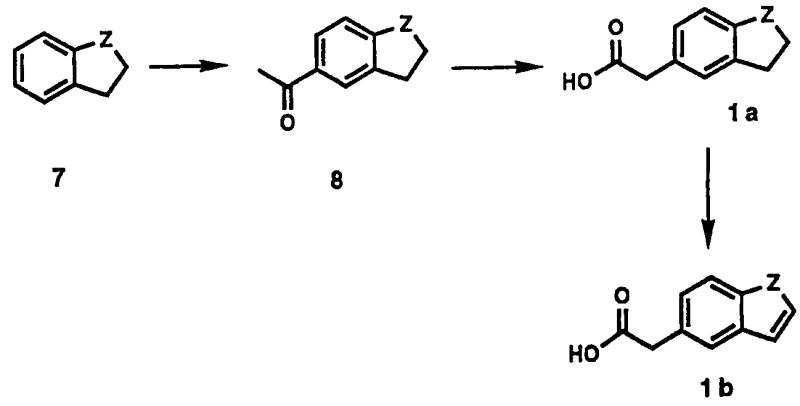

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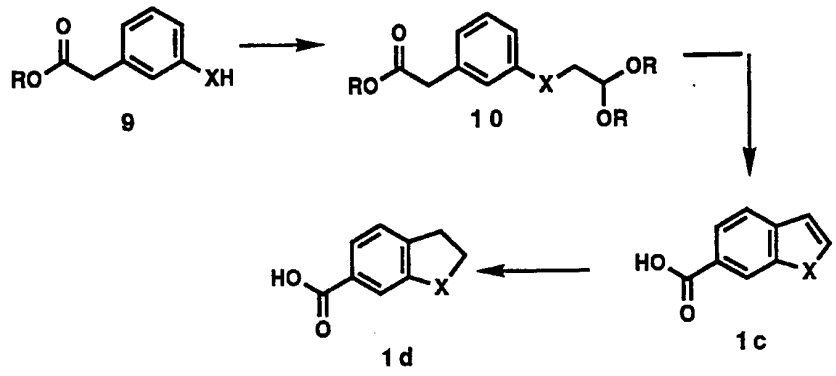

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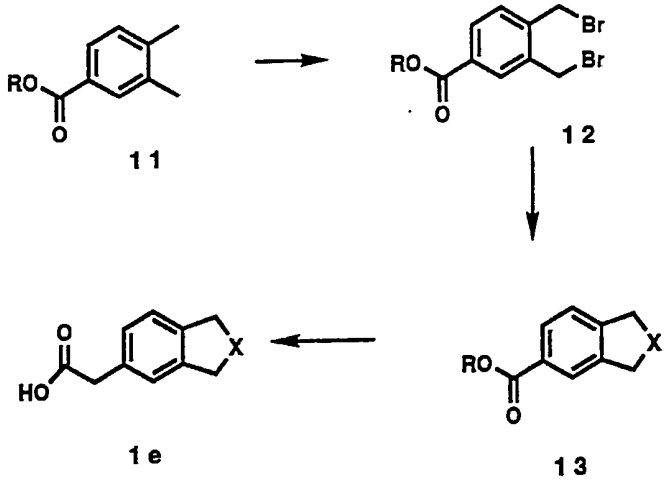
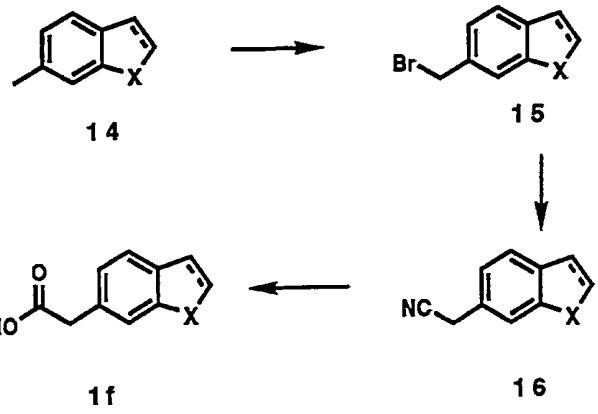
SCHEME 2C



11 12 13 1e

SCHEME 2D



14 15 16 1f

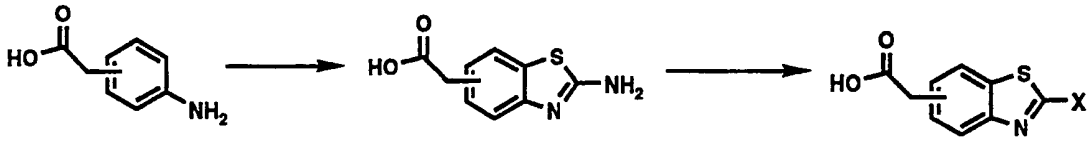
SCHEME 2E

17 1g

SCHEME 2F

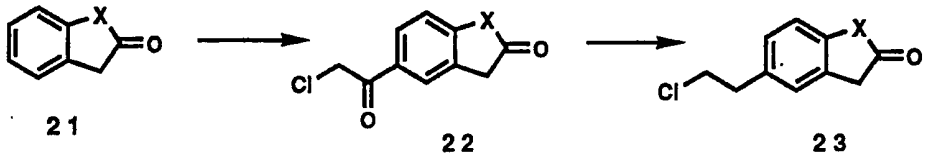
18 1h

SCHEME 2G



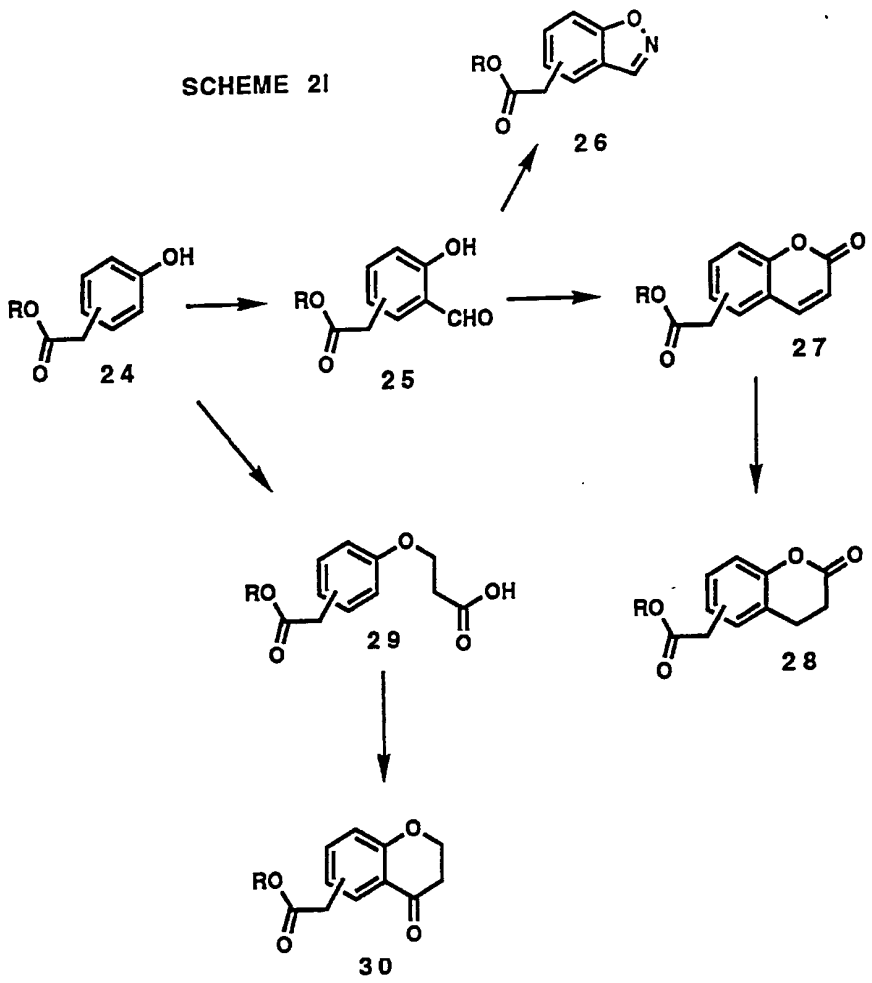
19 20 1i

SCHEME 2H



21 22 23

SCHEME 2I



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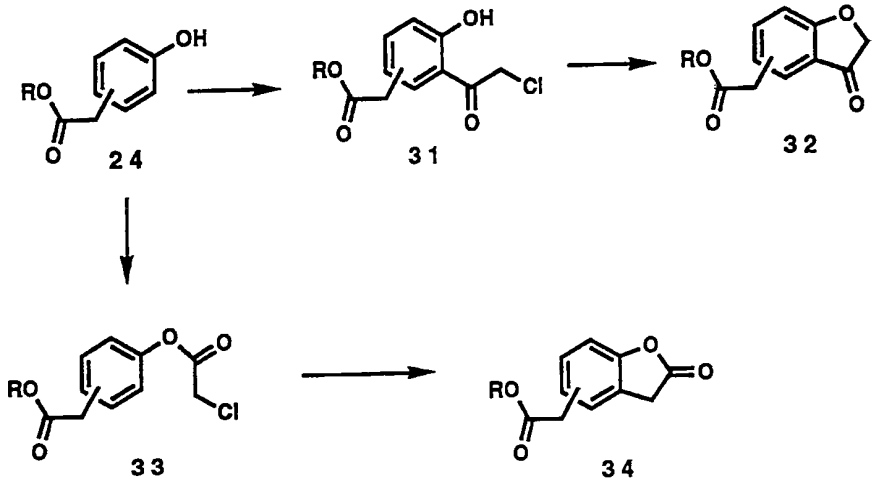

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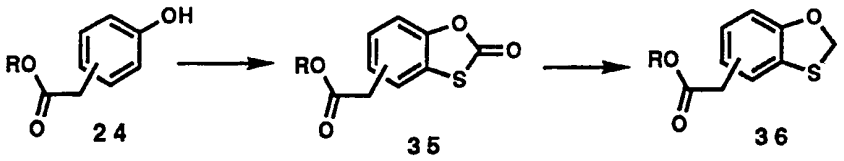

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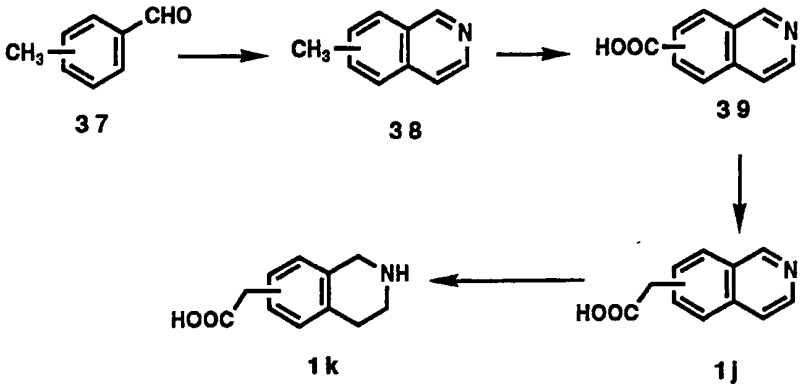

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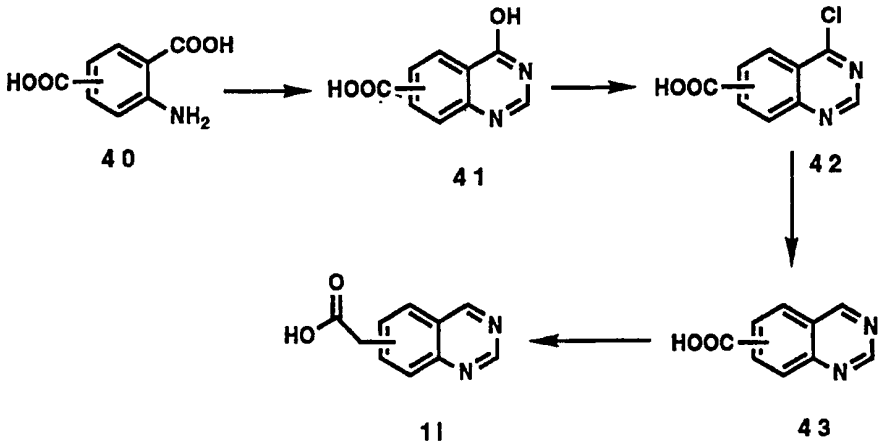
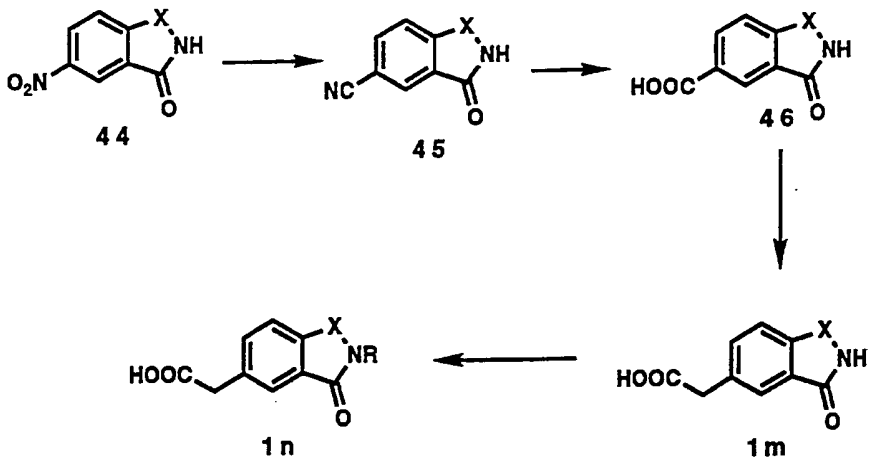


SCHEME 2N



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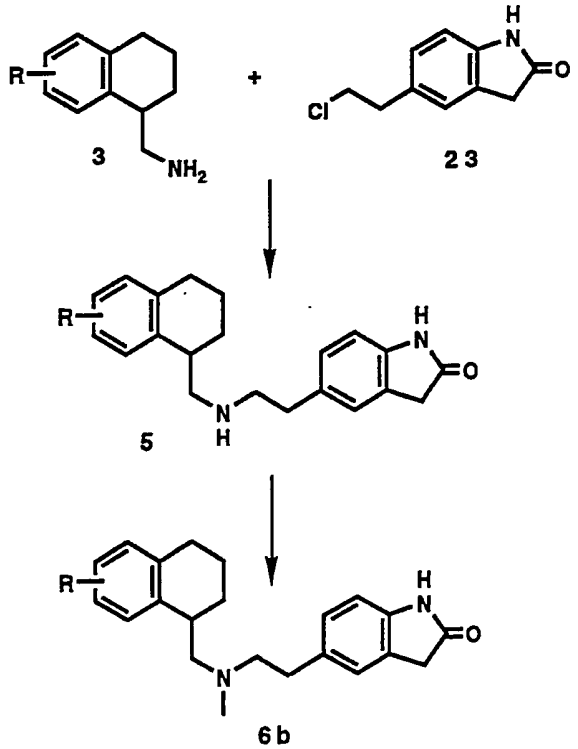

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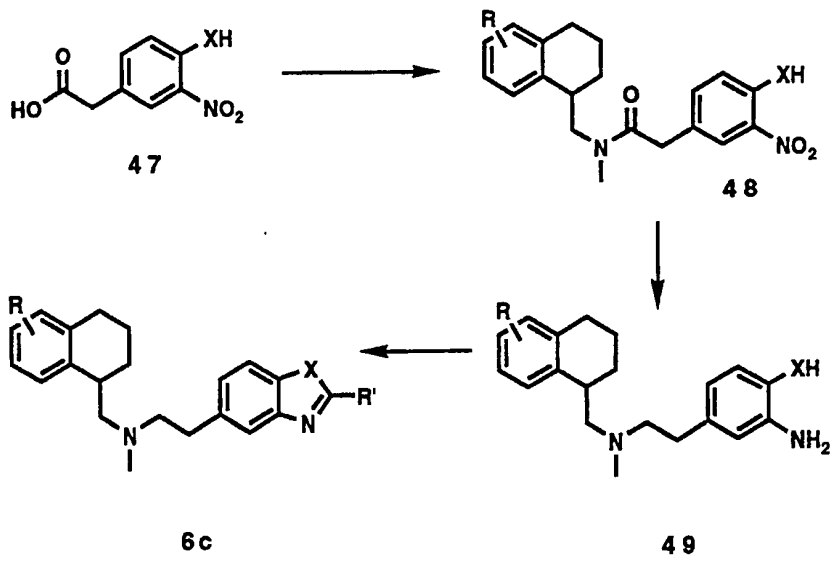
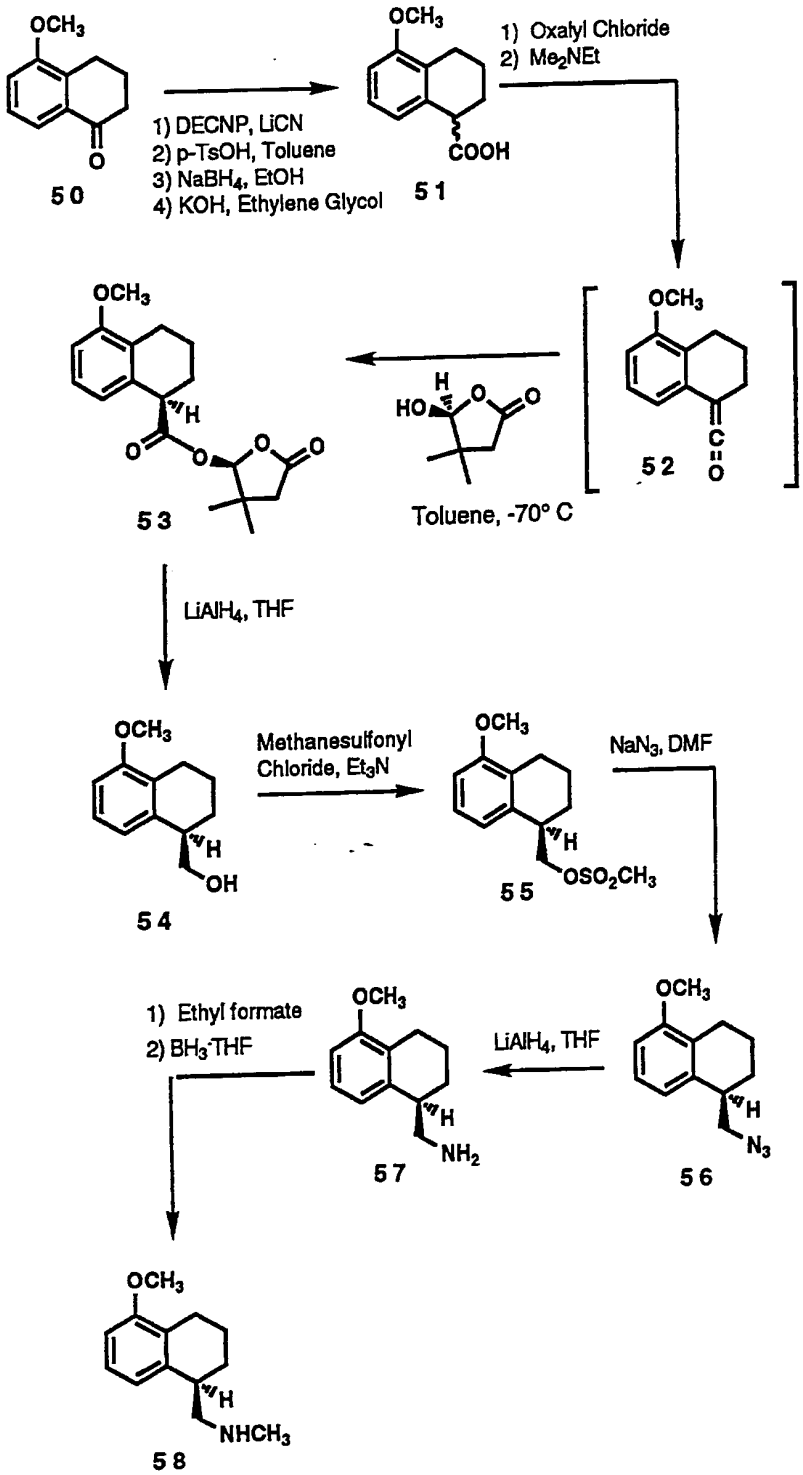
SCHEME 4



SCHEME 5


OCH3
O
50
1) DECNP, LiCN
2) p-TsOH, Toluene
3) NaBH4, EtOH
4) KOH, Ethylene Glycol
OCH3
COOH
51
1) Oxalyl Chloride
2) Me2NEt
OCH3
C=O
52
Toluene, -70° C
OCH3
H
O
O
O
53
LiAlH4, THF
OCH3
H
OH
54
Methanesulfonyl
Chloride, Et3N
OCH3
H
OSO2CH3
55
NaN3, DMF
OCH3
H
N3
56
LiAlH4, THF
1) Ethyl formate
2) BH3-THF
OCH3
H
NH2
57
OCH3
H
NHCH3
58

The following examples are provided for illustration and are not to be viewed as limiting the scope of the invention, and will serve to further illustrate preparation of the novel compounds of the invention. The following abbreviations are used: $CDCl_3$ for deuterochloroform, DMSO-d_6 for deuterodimethylsulfoxide, TMEDA for N,N,N',N'-tetramethylethylenediamine.

Example 1

(1R) and (1S)-5-Methoxy-1,2,3,4-tetrahydronaphthalene-1-carboxylic-(R)-(-)-phenylglycinol amide

To 5-methoxy-1,2,3,4-tetrahydronaphthalene-1-carboxylic acid, prepared by the procedure described in International Patent Application Number WO 89/06645, (1.03 g, 5.00 mmol) dissolved in methylene chloride (50 mL) was added oxalyl chloride (0.65 mL) and dimethylformamide (2 drops). After 1 hour at reflux, the solvent and excess reagent were evaporated. The resulting acid chloride was added to a solution of (R)-(-)-2-phenylglycinol (0.823 g, 6.00 mmol) and 1.4 mL triethylamine in methylene chloride (50 mL). After 1 hour, the reaction was quenched with dilute aqueous hydrochloric acid and extracted with methylene chloride. The combined organic extracts dried over magnesium sulfate and evaporated to dryness. The resulting solid was purified by chromatography on silica gel to yield 0.70 g of (1R)-5-methoxy-1,2,3,4-tetrahydronaphthalene-1-carboxylic-(R)-(-)-phenylglycinol amide. m.p. 179-180 °C. ^1H NMR ($CDCl_3$, 300 MHz) δ 1.75-2.0 (m, 3H), 2.3 (m, 1H), 2.39 (dd, 1H), 2.6 (m, 1H), 2.80 (dt, 1H), 3.70 (t, 1H), 3.79 (m, 2H), 3.84 (s, 3H), 5.1 (m, 1H), 6.05 (m, 1H), 6.75 (d, 1H), 6.77 (d, 1H), 7.13 (m, 3H), 7.3 (m, 3H). Further elution yielded 0.65 g of (1S)-5-methoxy-1,2,3,4-tetrahydro-naphthalene-1-carboxylic-(R)-(-)-phenylglycinol amide. m.p. 181-183 °C; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.6-2.0 (m, 3H), 2.3 (m, 1H), 2.57 (t, 1H), 2.6 (m, 1H), 2.76 (dt, 1H), 3.73 (t, 1H), 3.7 (m, 2H), 3.83 (s, 3H), 5.07 (m, 1H), 6.08 (m, 1H), 6.76 (d, 1H), 6.81 (d, 1H), 7.13 (m, 3H), 7.3 (m, 3H).

Example 2

(1R)-1-{N-[2-[(2R)-1-Hydroxy-2-phenyl]ethyl]aminomethyl}-5-methoxy-1,2,3,4-tetrahydronaphthalene hydrochloride

The (R,R) product resulting from Example 1 (7.18 g, 22 mmol) was dissolved in 100 mL tetrahydrofuran and 110 mL 1.0 *M* borane tetrahydrofuran complex and refluxed for 3.5 hours. The reaction was quenched by the addition of

methanol (50 mL) and the solvent evaporated. The residue obtained was dissolved in methanol (50 mL), and hydrogen chloride saturated isopropanol (25 mL) and refluxed for 30 minutes. The solvent was evaporated to yield 5.96 g of the desired product as a white solid. m.p. 157-158 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.4 (m, 1H), 1.76 (m, 1H), 2.25 (m, 1H), 2.4 (m, 1H), 2.62 (m, 1H), 2.97 (m, 1H), 3.1 (m, 1H), 3.52 (m, 1H), 3.75 (s, 3H), 4.08 (m, 1H), 4.5 (m, 2H), 5.62 (m, 1H), 6.62 (d, 1H), 6.73 (d, 1H), 7.03 (t, 1H), 7.43 (m, 3H), 7.7 (m, 2H), 9.5 (bs, 1H), 9,7 (bs, 1H). Anal calcd for $C_{20}H_{26}ClNO_2$: C, 69.05; H, 7.53; N, 4.03. Found: C, 68.66; H, 7.66; N, 4.02.

Example 3

(1S)-1-{N-[2-[(2R)-1-Hydroxy-2-phenyl]ethyl]aminomethyl}-5-methoxy-1,2,3,4-tetrahydronaphthalene hydrochloride

The (S,R) product resulting from Example 1 (4.6 g, 14 mmol) was treated by the procedure described in Example 2 to yield 4.0 g of the desired product as a white solid. m.p. 190-191 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.6-2.0 (m, 3H), 2.25 (m, 1H), 2.43 (m, 1H), 2.7 (m, 1H), 3.07 (m, 1H), 3.5 (m, 1H), 3.77 (s, 3H), 4.02 (m, 1H), 4.4 (m, 2H), 5.5 (m, 1H), 6.62 (d, 1H), 6.63 (d, 1H), 7.03 (t, 1H), 7.43 (m, 3H), 7.68 (m, 2H), 9.1 (m, 1H), 10.1 (m, 1H). Anal calcd for $C_{20}H_{26}ClNO_2$: C, 69.05; H, 7.53; N, 4.03. Found: C, 69.16; H, 7.56; N, 3.95.

Example 4

(R)-1-Aminomethyl-5-methoxy-1,2,3,4-tetrahydronaphthalene hydrochloride

The product resulting from Example 2 (3.22 g, 9.3 mmol) was dissolved in methanol (100 mL) and treated with hydrogen in the presence of palladium on carbon at 25 °C for 24 hours to yield 1.65 g of the desired product as a white solid. m.p. 266-267 °C. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 1.6-1.9 (m, 4H), 2.45 (m, 1H), 2.62 (dt, 1H), 2.92 (dd, 1H), 3.04 (m, 2H), 3.77 (s, 3H), 6.80 (d, 1H), 6.86 (d, 1H), 7.13 (t, 1H), 8.07 (bs, 3H). Anal calcd for $C_{12}H_{18}ClNO$: C, 63.29; H, 7.97; N, 6.15. Found: C, 63.64; H, 8.09; N, 6.17.

Example 5

(S)-(-)-1-Aminomethyl-5-methoxy-1,2,3,4-tetrahydronaphthalene hydrochloride

The product resulting from Example 3 (3.89 g, 11.2 mmol) was dissolved in methanol (100 mL) and treated with hydrogen in the presence of palladium on

carbon at 25 °C for 24 hours to yield 2.39 g of the desired product as a white solid. m.p. 267-269 °C. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 1.6-1.9 (m, 4H), 2.45 (m, 1H), 2.62 (dt, 1H), 2.92 (dd, 1H), 3.04 (m, 2H), 3.77 (s, 3H), 6.80 (d, 1H), 6.86 (d, 1H), 7.13 (t, 1H), 8.07 (bs, 3H). Anal calcd for $C_{12}H_{18}ClNO$: C, 63.29; H, 7.97; N, 6.15. Found: C, 63.56; H, 8.07; N, 6.16.

Example 6

(1R) and (1S)-5-Methoxy-8-fluoro-1,2,3,4-tetrahydronaphthalene-1-carboxylic-(R)-(-)-phenylglycinol amide

Step A

8-Fluoro-5-methoxy-3,4-dihydro-2H-1-naphthalenone

4-Fluoro-anisole (25 g, 198 mmol) and 48.8 g of ethyl succinyl chloride (298 mmol) were dissolved in 400 mL methylene chloride and cooled to 0 °C. To the reaction mixture was added 66 g of aluminum chloride over 15 minutes, and the reaction was then allowed to warm to 25 °C. After 18 hours, the reaction was quenched by pouring onto ice and the product isolated by extraction. The intermediate keto-ester was hydrogenated over a palladium catalyst in ethanol (200 mL) containing concentrated hydrochloric acid (10 mL) until the theoretical amount of hydrogen was consumed. After the catalyst was removed by filtration and the filtrate concentrated under reduced pressure, the intermediate ester was treated with aqueous potassium hydroxide solution (200 mL). Upon acidification, the intermediate acid was obtained. The acid was converted to its acid chloride by treatment with oxalyl chloride (17 mL) in methylene chloride catalyzed by 5 drops of dimethylformamide. The solvent was removed under reduced pressure and the acid chloride was redissolved in methylene chloride. Aluminum chloride (90 g) was added, and the reaction was stirred at 25 °C. for 18 hours. The reaction was quenched by pouring onto ice and the product extracted with ethyl acetate. The combined organic extracts were washed with water, dried over magnesium sulfate, and concentrated *in vacuo*. The residue obtained was recrystallized from hexane/ethyl acetate to yield 18.1 g of the title compound. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.1 (m, 2H), 2.62 (t, 2H), 2.89 (t, 2H), 3.83 (s, 3H), 6.95 (m, 2H).

Step B

8-Fluoro-5-methoxy-3,4-dihydro-naphthalen-1-carbonitrile

The tetralone resulting from Step A (5.4 g, 28 mmol) and diethylcyanophosphonate (6.8 g, 42 mmol) were dissolved in 40 mL tetrahydrofuran. To the reaction was added 100 mg lithium cyanide. After 1 hour, the reaction was quenched by pouring into water and extracted with several portions of ethyl acetate. The combined organic extracts were dried and concentrated under reduced pressure. The crude product was dissolved in 100 mL of toluene and 2 g *p*-toluenesulfonic acid was added. The reaction was refluxed for 30 minutes and then quenched in 5% sodium bicarbonate solution. After extraction with ethyl acetate, the combined organic extracts were dried and concentrated under reduced pressure to yield 6.1 g. Recrystallization from hexane/ethyl acetate gave 5.65 g of the title compound. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.43 (m, 2H), 2.80 (t, 2H), 3.81 (s, 3H), 6.81 (dd, 1H), 6.93 (dd, 1H), 7.0 (t, 1H).

Step C

(1R) and (1S)-5-Methoxy-8-fluoro-1,2,3,4-tetrahydronaphthalene-1-carboxylic-(R)-(-)-phenylglycinol amide

The compound resulting from Step B (4.3 g) was treated with sodium borohydride in refluxing ethanol, followed by potassium hydroxide hydrolysis in refluxing ethylene glycol to yield the 1-carboxylic acid intermediate. This compound was then coupled with (R)-(-)-phenylglycinol according to the procedure outlined in Example 1 to yield 4.46 g of a mixture of diastereomeric amides.

Example 7

(1R) and (1S)-1-{N-[2-[(2R)-1-Hydroxy-2-phenyl]ethyl]aminomethyl}-5-methoxy-8-fluoro-1,2,3,4-tetrahydronaphthalene hydrochloride

The diastereomeric mixture of amides from Example 6 (4.46 g) was treated by the procedure described in Example 2 to yield, after chromatographic separation, 1.4 g of the 1R isomer. m.p. 185-186 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) of the free base δ 1.5-1.8 (m, 4H), 1.9 (bs, 1H), 2.12 (m, 1H), 2.43 (m, 1H), 2.2 (m, 3H), 3.2 (m, 1H), 3.54 (dd, 1H), 3.71 (dd, 1H), 3.74 (s, 3H), 3.85 (dd, 1H), 6.57 (dd, 1H), 6.76 (t, 1H), 7.3 (m, 5H). Also obtained was 1.3 g of the 1S isomer. m.p. 189-190 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) of the free base δ 1.5-2.0 (m, 5H), 2.13 (m, 1H), 2.35-2.9 (m, 5H), 3.08 (m, 1H), 3.53 (dd, 1H), 3.7-3.8 (m, 2H), 3.76 (s, 3H), 6.56 (dd, 1H), 6.75 (t, 1H), 7.3 (m, 5H).

Example 8

(R)-1-Aminomethyl-5-methoxy-8-fluoro-1,2,3,4-tetrahydronaphthalene hydrochloride

The 1R isomer from Example 7 (1.3 g, 3.5 mmol) was treated by the procedure described in Example 4 to yield 0.76 g of the desired product as a white solid. m.p. 262-264 °C. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 1.5-1.8 (m, 4H), 2.0 (d, 1H), 2.38 (m, 1H), 3.2 (m, 1H), 3.3 (m, 2H), 3.72 (s, 3H), 6.81 (dd, 1H), 6.96 (t, 1H), 8.0 (bs, 3H). $[\alpha]_D^{25°} = +50.0°$ (acetic acid).

Example 9

(S)-(-)-1-Aminomethyl-5-methoxy-8-fluoro-1,2,3,4-tetrahydronaphthalene hydrochloride

The 1S isomer from Example 7 (1.22 g, 3.3 mmol) was treated by the procedure described in Example 4 to yield 0.69 g of the desired product as a white solid. m.p. 262-263 °C. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 1.5-1.8 (m, 4H), 2.0 (d, 1H), 2.38 (m, 1H), 3.2 (m, 1H), 3.3 (m, 2H), 3.72 (s, 3H), 6.81 (dd, 1H), 6.96 (t, 1H), 8.0 (bs, 3H). $[\alpha]_D^{25°} = -49.7°$ (acetic acid).

Example 10

(R)-5-Methoxy-1,2,3,4-tetrahydronaphthalene-1-carboxylic acid (R)-dihydro-3-hydroxy-4,4-dimethyl-2(3H)-furanone ester

Racemic 5-methoxy-1,2,3,4-tetrahydronaphthalene-1-carboxylic acid (46.31 g, 224.6 mmol) was dissolved in toluene (1 L). To the solution was added oxalyl chloride (21.6 mL, 247 mmol) and dimethylformamide (0.5 mL). After 1.5 hours at 50 °C, the solution was cooled to 10 °C and dimethylethyl amine (73 mL, 674 mmol) was added. The reaction was stirred at ambient temperature for 3 hours, and then cooled to -70 °C. (R)-Dihydro-3-hydroxy-4,4-dimethyl-2(3H)-furanone (35.1 g, 269.5 mmol) was added and the reaction was stirred for 2 hours, warming slowly to -30 °C. The reaction was then poured into water and extracted with ether. The combined organic extracts were washed with 5% sodium bicarbonate and brine, dried over magnesium sulfate and evaporated to dryness under reduced pressure. Trituration with 1:1 ether/hexane yielded 61.68 g (86%) of the desired product as a white solid. m.p. 74-77 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.97 (s, 3H), 1.17

(s, 3H), 1.7-2.2 (m, 4H), 2.7 (m, 2H), 3.80 (s, 3H), 3.98 (t, 1H), 4.01 (s, 2H), 4.40 (s, 1H), 6.72 (d, 1H), 6.83 (d, 1H), 7.12 (t, 1H).

Example 11

(R)-5-Methoxy-1,2,3,4-tetrahydronaphthalene-1-methanol

To lithium aluminum hydride (14.7 g, 387.2 mmol) suspended in tetrahydrofuran (400 mL) was added 61.65 g (196.6 mmol) of the product resulting from Example 10 dissolved in tetrahydrofuran (200 mL) over 30 minutes. After an additional 1 hour, the reaction was quenched using the Fieser workup conditions, filtered through Celite, and evaporated to dryness to yield 36.98 g (98%) of the desired product as a colorless oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.54 (bs, 1H), 1.7-2.0 (m, 4H), 2.5-2.7 (m, 2H), 2.97 (m, 1H), 3.80 (d, 2H), 3.81 (s, 3H), 6.70 (d, 1H), 6.86 (d, 1H), 7.12 (t, 1H).

Example 12

(R)-5-Methoxy-1,2,3,4-tetrahydronaphthalene-1-methanol-methanesulfonate ester

The product resulting from Example 11 (36.98 g, 192.3 mmol) was dissolved in methylene chloride (600 mL) and triethylamine (53.6 mL, 385 mmol). The solution was cooled to 0 °C, and methanesulfonyl chloride (17.85 mL, 230.7 mmol) was added over 15 minutes. After 1 hour at 0 °C, the reaction was poured into water and extracted with methylene chloride. The combined organic extracts were washed with 5% sodium bicarbonate and brine, dried over magnesium sulfate, and evaporated to dryness to yield 49.05 g (94%) of the desired product as a light yellow solid. m.p. 55-56 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.7-2.0 (m, 4H), 2.56 (m, 1H), 2.75 (dt, 1H), 2.98 (s, 3H), 3.22 (m, 1H), 3.81 (s, 3H), 4.28 (t, 1H), 4.40 (dd, 1H), 6.71 (d, 1H), 6.81 (d, 1H), 7.12 (t, 1H).

Example 13

(R)-5-Methoxy-1-azidomethyl-1,2,3,4-tetrahydronaphthalene

The product resulting from Example 12 (49.05 g, 181.5 mmol) was dissolved in dimethylformamide (250 mL). To the solution was added sodium azide (27.4 g, 421.5 mmol) and the solution was stirred at 60 °C for 18 hours. The reaction was quenched with water and extracted with ether. The combined organic extracts were washed with water and brine, dried over magnesium sulfate and evaporated to dryness to yield 35.46 g (90%) of the desired product as a light yellow solid. m.p. 65-66 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.7-2.0 (m, 4H),

2.58 (m, 1H), 2.71 (dt, 1H), 3.03 (m, 1H), 3.41 (dd, 1H), 3.59 (dd, 1H), 3.80 (t, 3H), 6.70 (d, 1H), 6.80 (d, 1H), 7.12 (t, 1H).

Example 14

(R)-1-Aminomethyl-5-methoxy-1,2,3,4-tetrahydronaphthalene hydrochloride

The product resulting from Example 13 (35.46 g, 163.2 mmol) was dissolved in tetrahydrofuran (150 mL) and added to a suspension of lithium aluminum hydride (12.4 g, 326 mmol) in tetrahydrofuran (400 mL). After 1 hour, the reaction was quenched by the addition of water, filtered, and evaporated to dryness. Conversion to the hydrochloric acid salt and recrystallization from ethanol yielded 32.11 g (86%) of the desired product as a white solid. m.p. 266-267 °C. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 1.6-1.9 (m, 4H), 2.45 (m, 1H), 2.62 (dt, 1H), 2.92 (dd, 1H), 3.04 (m, 2H), 3.77 (s, 3H), 6.80 (d, 1H), 6.86 (d, 1H), 7.13 (t, 1H), 8.07 (bs, 3H). $[\alpha]_D^{25°} = +26.1°$ (acetic acid).

Example 15

N-[(R)-5-Methoxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]-N-methylamine hydrochloride

The product resulting from Example 14 (32.1 g, 141 mmol) was converted to its free base and refluxed in toluene (250 mL) and ethyl formate (250 mL) for 18 hours. The solvent was evaporated under reduced pressure and the product dissolved in tetrahydrofuran (250 mL). Borane (1.0 *M* in tetrahydrofuran, 564 mL) was added and the reaction was refluxed for 5 hours. After cooling to ambient temperature, methanol (50 mL) was added and solvent was evaporated under reduced pressure. To the product was added methanol (200 mL) and isopropanol saturated with anhydrous hydrogen chloride (100 mL). After refluxing for 2 hours, the solvent was evaporated *in vacuo* and the product was recrystallized from ethanol to yield 29.5 g of the desired product. m.p. 214-215 °C. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 1.65-1.9 (m, 4H), 2.4-2.7 (m, 2H), 2.59 (s, 3H), 3.0-3.3 (m, 3H), 3.76 (s, 3H), 6.81 (d, 1H), 6.87 (d, 1H), 7.14 (t, 1H), 8.7 (bs, 2H).

Example 16

N-[(R)-5-Methoxy-8-fluoro-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]-N-methylamine hydrochloride

The title compound was prepared from 5-methoxy-8-fluoro-1,2,3,4-tetrahydronaphthalene-1-carboxylic acid, the compound resulting from the first part

in Step C, by the procedures described in Examples 10 through 15 to yield the product as a white solid. m.p. 248-250 °C. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 1.5-1.8 (m, 4H), 2.1 (m, 1H), 2.4 (m, 1H), 2.6 (t, 3H), 2.7 (m, 1H), 2.93 (m, 1H), 3.12 (m, 1H), 3.76 (s, 3H), 6.84 (dd, 1H), 7.0 (t, 1H), 8.9 (bs, 2H).

Example 17

N-[(R)-5-Ethoxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]-N-methylamine hydrochloride

5-Ethoxy-1-tetralone was prepared from the commercially available 5-methoxy-1-tetralone by treatment with $AlCl_3$ in benzene followed by alkylation of the resulting phenol with ethyl iodide in acetone in the presence of potassium carbonate. The resulting tetralone was then treated by the procedures described in International Patent Application Number WO 89/06645 for the preparaton of 5-methoxy 1,2,3,4-tetrahydronaphthalene-1-carboxylic acid to yield 5-ethoxy-1,2,3,4-tetrahydronaphthalene-1-carboxylic acid. The title compound was prepared from 5-ethoxy-1,2,3,4-tetrahydronaphthalene-1-carboxylic acid by the procedures described in Examples 10 through 15 to yield the product as a white solid. m.p. 219-221 °C. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 1.32 (t, 3H), 1.65-1.9 (m, 4H), 2.4-2.7 (m, 2H), 2.59 (s, 3H), 3.0-3.3 (m, 3H), 4.0 (m, 2H), 6.78 (d, 1H), 6.84 (d, 1H), 7.12 (t, 1H), 8.6 (bs, 2H).

Example 18

N-[(R)-5,6-Methylenedioxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]-N-methylamine hydrochloride

5,6-Methylenedioxy-1,2,3,4-tetrahydronaphthalene-1-carboxylic acid was prepared by the procedure described in International Patent Application Number WO 89/06645, and treated as described in Examples 10 through 15 to yield the product as a white solid. m.p. 225-257 °C. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 1.6-1.9 (m, 4H), 2.5-2.7 (m, 2H), 2.58 (s, 3H), 3.06 (m, 2H), 3.16 (m, 1H), 5.97 (d, 2H), 6.77 (d, 1H), 6.79 (D, 1H), 8.8 (bs, 2H).

Example 19

N-[2-(2,3-Dihydrobenzofuran-5-yl)ethyl]-N-[(R)--5-methoxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]-N-methylamine methanesulfonate

2,3-Dihydrobenzofuran-5-acetic acid (0.98 g, 5.5 mmol) and the product resulting from Example 15 (1.21 g, 5.0 mmol) were combined with 1-(3-

dimethylaminopropyl)-3-ethyl carbodiimide hydrochloride (1.15 g, 6.0 mmol), 1-hydroxybenzotriazole (1.01 g, 67.5 mmol) and triethylamine (5.5 mmol, 0.8 mL) in tetrahydrofuran (50 mL) and the reaction was stirred for 18 hours at 25 °C. The product was isolated and treated with 1.0 *M* borane in tetrahydrofuran (20 mL) at reflux for 4 hours. After isolation of the desired product, treatment with 1.1 equivalents of methanesulfonic acid and recrystallization from ethyl acetate yielded 1.29 g of the desired product as a white solid. m.p. 161-163 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.7-2.2 (m, 4H), 2.5-3.5 (m, 9H), 2.86 (s, 3H), 3.00 (d, 3H), 3.18 (t, 2H), 3.81 (s, 3H), 4.55 (t, 2H), 6.71 (m, 3H), 6.94 (dd, 1H), 7.15 (m, 2H), 10.8 (bs, 1H). Anal calcd for $C_{24}H_{33}NO_5S$: C, 64.40; H, 7.43; N, 3.13. Found: C, 64.33; H, 7.36; N, 3.06.

Example 20

N-[2-(Benzofuran-5-yl)ethyl]-N-[5-methoxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]-N-methylamine methanesulfonate

Benzofuran-5-acetic acid (0.54 g) and N-5-methoxy-1,2,3,4-tetrahydro-naphthalen-1-ylmethyl]-N-methylamine hydrochloride (0.57 g, prepared as described in published PCT patent application WO 89/06645) were treated as described in Example 19 to yield 0.52 g of the desired product as a white solid. m.p. 156-157 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) of the free base δ 1.6-1.8 (m, 3H), 1.95 (m, 1H), 2.40 (s, 3H), 2.4-3.0 (m, 9H), 3.81 (s, 3H), 6.66 (d, 1H), 6.70 (d, 1H), 6.81 (d, 1H), 7.08 (t, 1H), 7.12 (dd, 1H), 7.4 (d, 1H), 7.41 (s, 1H), 7.59 (d, 1H). Anal calcd for $C_{24}H_{31}NO_6S$: C, 64.69; H, 7.01; N, 3.14. Found: C, 64.51; H, 6.88; N, 3.13.

Example 21

N-[2-(2,3-Dihydrobenzofuran-5-yl)ethyl]-N-[(R)-5-methoxy-8-fluoro-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]-N-methylamine methanesulfonate

2,3-Dihydrobenzofuran-5-acetic acid (0.62 g) and the product resulting from Example 16 (0.75 g) were treated by the procedure described in Example 19 to yield 0.805 g of the desired product as a white solid. m.p. 130-132 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) of the free base δ 1.7-2.1 (m, 4H), 2.4-2.5 (m, 2H), 2.8-3.6 (m, 7H), 2.85 (s, 3H), 3.02 (d, 3H), 3.18 (t, 2H), 3.80 (s, 3H), 4.56 (t, 2H), 6.6-7.0 (m, 4H), 7.13 (d, 1H), 10.9 (bs, 1H). Anal calcd for $C_{24}H_{32}FNO_5S$: C, 61.92; H, 6.93; N, 3.01. Found: C, 62.15; H, 6.95; N, 3.00.

Example 22

N-[2-(Benzofuran-6-yl)ethyl]-N-[(R)-5-methoxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]-N-methylamine methanesulfonate

Benzofuran-6-acetic acid (0.63 g) and the product resulting from Example 15 (0.61 g) were treated by the procedure described in Example 19 to yield 0.23 g of the desired product as a white solid. m.p. 191-193 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) of the free base δ 1.6-2.0 (m, 4H), 2.4 (s, 3H), 2.3-3.0 (m, 9H), 3.81 (s, 3H), 6.67 (d, 1H), 6.72 (dd, 1H), 6.80 (d, 1H), 7.09 (m, 2H), 7.36 (s, 1H), 7.49 (d, 1H), 7.57 (d, 1H). Anal calcd for $C_{24}H_{31}NO_5S$: C, 64.69; H, 7.01; N, 3.14. Found: C, 64.59; H, 6.91; N, 3.11.

Example 23

N-[2-(2,3-Dihydrobenzofuran-5-yl)ethyl]-N-[(R)-5-ethoxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]-N-methylamine methanesulfonate

2,3-Dihydrobenzofuran-5-acetic acid (0.43 g) and the product resulting from Example 17 (0.50 g) were treated by the procedure described in Example 19 to yield 0.49 g of the desired product as a white solid. m.p. 152-153 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.32 (t, 3H), 1.7-2.2 (m, 4H), 2.5-3.5 (m, 9H), 2.86 (s, 3H), 3.00 (d, 3H), 3.18 (t, 2H), 4.0 (m, 2H), 4.55 (t, 2H), 6.71 (m, 3H), 6.94 (dd, 1H), 7.15 (m, 2H), 10.8 (bs, 1H). Anal calcd for $C_{25}H_{35}NO_5S$: C, 65.05; H, 7.64; N, 3.03. Found: C, 65.04; H, 7.60; N, 3.01.

Example 24

N-[2-(2,3-Dihydrobenzofuran-6-yl)ethyl]-N-[(R)-5-methoxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]-N-methylamine hydrochloride

2,3-Dihydrobenzofuran-6-acetic acid (0.31 g) and the product resulting from Example 15 (0.50 g) were treated by the procedure described in Example 19, converting instead to the hydrochloride salt, to yield 0.31 g of the desired product as a white solid. m.p. 227-229 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) of the free base δ 1.6-2.0 (m, 4H), 2.38 (s, 3H), 2.4-3.0 (m, 9H), 3.17 (t, 2H), 3.81 (s, 3H), 4.54 (t, 2H), 6.68 (m, 3H), 6.80 (d, 1H), 7.10 (m, 2H). Anal calcd for $C_{23}H_{30}NO_2Cl$: C, 71.21; H, 7.79; N, 3.61. Found: C, 71.68; H, 7.87; N, 3.54.

Example 25

N-[2-(2,3-Dihydrobenzofuran-5-yl)ethyl]-N-[(R)-5,6-methylenedioxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]-N-methylamine methanesulfonate

2,3-Dihydrobenzofuran-5-acetic acid (0.68 g) and the product resulting from Example 18 (0.80 g) were treated by the procedure described in Example 19 to yield 1.08 g of the desired product as a white solid. m.p. 175-176 °C. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 1.7-1.9 (m, 4H), 2.3 (s, 3H), 2.4-3.5 (m, 9H), 2.93 (d, 3H), 3.17 (t, 2H), 4.54 (t, 2H), 5.95 (s, 2H), 6.7-7.0 (m, 5H), 9.1 (bs, 1H). Anal calcd for $C_{24}H_{31}NO_6S$: C, 62.45; H, 6.77; N, 3.04. Found: C, 62.79; H, 6.81; N, 3.01.

Example 26

N-[2-(2,3-Dihydrobenzo[b]thien-5-yl)ethyl]-N-[(R)-5-methoxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]-N-methylamine methanesulfonate

2,3-Dihydrobenzothiophene-5-acetic acid (0.80 g) and the product resulting from Example 15 (0.72 g) were treated by the procedure described in Example 19 to yield 0.33 g of the desired product as a white solid. m.p. 158-159 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) of the free base δ 1.6-1.8 (m, 3H), 1.94 (m, 1H), 2.38 (s, 3H), 2.3-3.0 (m, 9H), 3.2-3.4 (m, 4H), 3.82 (s, 3H), 6.67 (d, 1H), 6.80 (d, 1H), 6.94 (dd, 1H), 7.1 (m, 3H). Anal calcd for $C_{24}H_{33}NO_5S_2$: C, 62.17; H, 7.17; N, 3.02. Found: C, 63.77; H, 7.62; N, 3.05.

Example 27

N-[2-(Benzimidazol-5-yl)ethyl]-N-[(R)-5-methoxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]-N-methylamine bis-methanesulfonate

4-Amino-3-nitrophenylacetic acid (0.97 g) and the product resulting from Example 15 (1.0 g) were treated by the procedure described in Example 19. The intermediate product was hydrogenated using a palladium catalyst in ethanol to yield the intermediate dianiline. Reluxing of this intermediate with formic acid (1.2 equivalents) in 10% aqueous hydrochloric acid for 1 hour, followed by isolation and conversion to the bis-methanesulfonate salt yielded 0.61 g of the desired product as a white solid. m.p. 162-164 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) of the free base δ 1.6-1.8 (m, 3H), 1.94 (m, 1H), 2.39 (s, 3H), 2.4-3.0 (m, 9H), 3.80 (s, 3H), 6.67 (d, 1H), 6.81 (d, 1H), 7.08 (t, 1H), 7.13 (dd, 1H), 7.47 (bs, 1H), 7.59 (bs, 1H), 8.01 (s, 1H), 9.5 (bs, 1H). Anal calcd for $C_{24}H_{35}N_3O_7S_2$: C, 53.30; H, 6.30; N, 7.80. Found: C, 52.93; H, 6.60; N, 7.62.

Example 28

N-[2-(Benzoxazol-6-yl)ethyl]-N-[(R)-5-methoxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]-N-methylamine methanesulfonate

4-Nitro-3-hydroxyphenylacetic acid (0.711 g) and the product resulting from Example 15 (0.725 g) were treated by the procedure described in Example 19. The intermediate product was hydrogenated using a palladium catalyst in ethanol to yield the intermediate amino-phenol. Treatment of this intermediate with triethylorthoformate at reflux for 18 hours, followed by isolation and conversion to the methanesulfonate salt yielded 0.54 g of the desired product as a white solid. m.p. 139-141 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.7-2.3 (m, 5H), 2.5-3.6 (m, 8H), 2.89 (s, 3H), 3.06 (d, 3H), 3.82 (s, 3H), 6.7 (m, 2H), 7.13 (t, 1H), 7.27 (dd, 1H), 7.55 (bs, 1H), 7.72 (d, 1H), 8.09 (s, 1H), 11.0 (bs, 1H). Anal calcd for $C_{23}H_{30}N_2O_5S$: C, 61.86; H, 6.77; N, 6.27. Found: C, 61:60; H, 6.40; N, 6.19.

Example 29

N-[2-(Benzoxazol-5-yl)ethyl]-N-[(R)-5-methoxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]-N-methylamine methanesulfonate

3-Nitro-4-hydroxyphenylacetic acid and the product resulting from Example 15 were treated by the procedure described in Example 19. The intermediate product was hydrogenated using a palladium catalyst in ethanol to yield the intermediate amino-phenol. Treatment of this intermediate with triethyl orthoformate at reflux for 1 hour, followed by isolation and conversion to the methanesulfonate salt yielded the desired product as a white solid. m.p. 175-177 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) of the free base δ 1.6-1.8 (m, 3H), 1.93 (m, 1H), 2.39 (s, 3H), 2.4-3.0 (m, 9H), 3.81 (s, 3H), 6.67 (d, 1H), 6.80 (d, 1H), 7.09 (t, 1H), 7.22 (dd, 1H), 7.47 (d, 1H), 7.62 (d, 1H), 8.08 (s, 1H). Anal calcd for $C_{23}H_{30}N_2O_5S$: C, 61.86; H, 6.77; N, 6.27. Found: C, 61.98; H, 6.82; N, 6.28.

Example 30

N-[2-(Benzoxazol-6-yl)ethyl]-N-[(R)-8-fluoro-5-methoxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]-N-methylamine methanesulfonate

4-Nitro-3-hydroxyphenylacetic acid (0.91 g) and the product resulting from Example 16 (1.0 g) were treated by the procedure described in Example 19. The intermediate product was hydrogenated using a palladium catalyst in ethanol to yield

the intermediate amino-phenol. Treatment of this intermediate with triethylorthoformate at reflux for 18 hours, followed by isolation and conversion to the methanesulfonate salt yielded 0.84 g of the desired product as a white solid. m.p. 180-181 °C. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 1.55-1.85 (m, 3H), 2.05 (m, 1H), 2.31 (s, 3H), 2.3-3.6 (m, 9H), 3.0 (d, 3H), 3.78 (s, 3H), 6.87 (dd, 1H), 7.02 (t, 1H), 7.38 (dd, 1H), 7.25 (dd, 1H), 7.32 (d, 1H), 8.75 (s, 1H), 9.3 (bs, 1H). Anal calcd for $C_{23}H_{29}FN_2O_5S$: C, 59.47; H, 6.29; N, 6.03. Found: C, 59.41; H, 6.40; N, 5.92.

Example 31

N-[2-(Benzoxazol-5-yl)ethyl]-N-[(R)-8-fluoro-5-methoxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]-N-methylamine methanesulfonate

3-Nitro-4-hydroxyphenylacetic acid (0.80 g) and the product resulting from Example 16 (0.88 g) were treated by the procedure described in Example 19. The intermediate product was hydrogenated using a palladium catalyst in ethanol to yield the intermediate amino-phenol. Treatment of this intermediate with triethylorthoformate at reflux for 18 hours, followed by isolation and conversion to the methanesulfonate salt yielded 0.29 g of the desired product as a white solid. m.p. 166-167 °C. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 1.55-1.85 (m, 3H), 2.05 (m, 1H), 2.31 (s, 3H), 2.3-3.6 (m, 9H), 3.0 (d, 3H), 3.78 (s, 3H), 6.87 (dd, 1H), 7.03 (t, 1H), 7.4 (dd, 1H), 7.25 (dd, 1H), 7.30 (d, 1H), 8.75 (s, 1H), 9.3 (bs, 1H). Anal calcd for $C_{23}H_{29}FN_2O_5S$: C, 59.47; H, 6.29; N, 6.03. Found: C, 59.52; H, 6.31; N, 5.92.

Example 32

N-[2-([4H]-2,3-Dihydrobenzopyran-6-yl)ethyl]-N-[(R)-5-methoxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]-N-methylamine methanesulfonate

[4H]-2,3-Dihydrobenzopyran-6-acetic acid (0.50 g) and the product resulting from Example 15 (0.48 g) were treated by the procedure described in Example 19 to yield 0.10 g of the desired product as a white solid. m.p. 171-172 °C. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 1.7-2.0 (m, 6H), 2.3 (s, 3H), 2.4-3.5 (m, 11H), 2.95 (d, 3H), 3.77 (s, 3H), 6.6-7.2 (m, 6H), 9.1 (bs, 1H). Anal calcd for $C_{25}H_{35}NO_5S$: C, 65.05; H, 7.64; N, 3.03. Found: C, 65.07; H, 7.66; N, 2.96.

Example 33

N-[2-(Indan-5-yl)ethyl]-N-[(R)-5-methoxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]-N-methylamine methanesulfonate

Indan-5-acetic acid (1.0 g) and the product resulting from Example 15 (0.96 g) were treated by the procedure described in Example 19 to yield 1.18 g of the desired product as a white solid. m.p. 170-172 °C. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 1.7-2.1 (m, 6H), 2.31 (s, 3H), 2.4-3.5 (m, 13H), 2.96 (d, 3H), 3.77 (s, 3H), 6.82 (d, 1H), 6.87 (d, 1H), 7.0-7.3 (m, 4H), 9.1 (bs, 1H). Anal calcd for $C_{25}H_{35}NO_4S$: C, 67.38; H, 7.92; N, 3.14. Found: C, 67.82; H, 7.85; N, 3.14 .

Example 34

N-[2-(N-Methanesulfonamido-2,3-dihydroindol-5-yl)ethyl]-N-[(R)-5-methoxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]-N-methylamine methanesulfonate

N-Methanesulfonamido-2,3-dihydroindole-5-acetic acid (1.14 g) and the product resulting from Example 15 (0.90 g) were treated by the procedure described in Example 19 to yield 0.98 g of the desired product as a white solid. m.p. 202-203 °C. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 1.7-1.9 (m, 4H), 2.7 (s, 3H), 2.4-2.6 (m, 2H), 2.93 (d, 3H), 2.95 (s, 3H), 2.9-3.6 (m, 9H), 3.78 (s, 3H), 3.92 (m, 2H), 6.81 (d, 1H), 6.87 (d, 1H), 7.07-7.3 (m, 4H), 9.1 (bs, 1H). Anal calcd for $C_{25}H_{36}N_2O_6S_2$: C, 57.23; H, 6.92; N, 5.34. Found: C, 57.25; H, 6.88; N, 5.30.

Example 35

N-[2-(Benzimidazol-5-yl)ethyl]-N-[(R)-8-fluoro-5-methoxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]-N-methylamine bis methanesulfonate monohydrate

4-Amino-3-nitrophenylacetic acid (0.82 g) and the product resulting from Example 16 (0.91 g) were treated by the procedure described in Example 19. The intermediate product was hydrogenated using a palladium catalyst in ethanol to yield the intermediate dianiline. Treatment of this intermediate with formic acid (1.2 equivalents) in 10% aqueous hydrochloric acid at reflux for 1 hour, followed by isolation and conversion to the bis-methanesulfonate salt yielded 0.63 g of the desired product as a white solid. m.p. 128-130° C. ^{1}H NMR ($CDCl_3$, 300 MHz) of the free base δ 1.4-1.8 (m, 3H), 2.1 (m, 1H), 2.4 (s, 3H), 2.3-3.0 (m, 9H), 3.2 (m, 1H), 3.79 (s, 3H), 6.6 (dd, 1H), 6.8 (t, 1H), 7.16 (dd, 1H), 7.48 (bs, 1H), 7.59 (bs, 1H), 8.02 (s, 1H). Anal calcd for $C_{24}H_{34}FN_3O_7S_2 \cdot H_2O$: C, 49.90; H, 6.28; N, 7.27. Found: C, 49.68; H, 6.00; N, 7.10.

Example 36

N-[2,3-Dihydroindol-5-yl)ethyl]-N-[(R)-5-methoxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]-N-methylamine bis-methanesulfonate

N-Benzoyl-2,3-dihydroindolyl-5-acetic acid (0.98 g) and the product resulting from Example 15 (0.85 g) were treated by the procedure described in Example 19 to yield the intermediate N-benzyl analog of the title compound as its dihydrochloride salt. Hydrogenation of this intermediate using a palladium catalyst in methanol afforded, after conversion to its methanesulfonate salt, 0.60 g of the desired product as a white solid. m.p. 207-208 °C.. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 1.7-2.0 (m, 4H), 2.3 (s, 6H), 2.4-2.7 (m, 2H), 2.96 (d, 3H), 3.0-3.7 (m, 12H), 3.77 (s, 3H), 6.82 (d, 1H), 6.88 (d, 1H), 7.1-7.4 (m, 4H), 9.2 (bs, 2H). Anal calcd for $C_{25}H_{38}N_2O_7S_2$: C, 55.33; H, 7.06; N, 5.16. Found: C, 55.20; H, 7.06; N, 5.05.

Example 37

N-[2-(2-Chlorobenzothiazol-6-yl)ethyl]-N-[(R)-5-methoxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]-N-methylamine methanesulfonate

2-Chlorobenzothiazole-6-acetic acid (0.33 g) and the product resulting from Example 15 (0.31 g) were treated by the procedure described in Example 19. The intermediate borane reduction product, prior to treatment with hydrochloric acid, was evaporated, suspended in ether and treated with TMEDA (tetramethylethylenediamine) (1.2 equiv.) at reflux for 4 hours. After filtration and purification by column chromatography, the product was converted to its methanesulfonate salt to yield 0.23 g of the desired product as a white solid. m.p. 153-154 °C. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 1.7-1.9 (m, 4H), 2.3 (s, 3H), 3.0 (d, 3H), 3.1-3.5 (m, 9H), 3.77 (s, 3H), 6.83 (d, 1H), 6.87 (d, 1H), 7.15 (t, 1H), 7.5 (dd, 1H), 7.97 (d, 1H), 8.04 (d, 1H), 9.3 (bs, 1H). Anal calcd for $C_{23}H_{29}ClN_2O_4S_2$: C, 55.38; H, 5.88; N, 5.63. Found: C, 55.03; H, 5.75; N, 5.49.

Example 38

N-[2-(Quinoxalin-6-yl)ethyl]-N-[(R)-5-methoxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]-N-methylamine methanesulfonate

4-Amino-3-nitrophenylacetic acid (0.97 g) and the product resulting from Example 15 (1.0 g) were treated by the procedure described in Example 19. The intermediate product was hydrogenated over palladium in ethanol to yield the intermediate dianiline. Treatment of this intermediate with 2,3-dihydroxy-1,4-dioxane, followed by conversion to the methanesulfonate addition salt yielded 0.88 g. of the desired product. m.p. 192 °C. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 1.7-2.0 (m, 4H), 2.3 (s, 3H), 2.4-3.6 (m, 9H), 3.03 (d, 3H), 3.79 (s, 3H), 6.84 (d, 1H), 6.90 (d, 1H), 7.16 (t, 1H), 7.85 (dd, 1H), 8.1 (m, 2H), 8.96 (m, 2H), 9.1 (bs, 1H). Anal calcd for $C_{24}H_{31}N_3O_4S$: C, 62.99; H, 6.83; N, 9.18. Found: C, 62.79; H, 6.96; N, 9.00.

Example 39

N-[2-(Quinolin-6-yl)ethyl]-N-[(R)-5-methoxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]-N-methylamine dihydrochloride dihydrate

Quinoline-6-acetic acid (1.0 g) and the product resulting from Example 15 (0.95 g) were treated by the procedure described in Example 19 to yield 0.79 g of the desired product as a white solid. m.p. 137-139 °C. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 1.6-2.7 (m, 7H), 2.95 (d, 3H), 3.2-3.7 (m, 6H), 3.79 (s, 3H), 6.80 (d, 1H), 6.92 (d, 1H), 7.15 (t, 1H), 7.85-8.3 (m, 4H), 8.82 (m, 1H), 9.14 (m, 1H). Anal calcd for $C_{24}H_{30}ClN_2O \cdot 2H_2O$: C, 61.40; H, 7.30; N, 5.96. Found: C, 61.13; H, 7.02; N, 5.89.

Example 40

N-[2-(Quinolin-7-yl)ethyl]-N-[(R)-5-methoxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]-N-methylamine dihydrochloride

Quinoline-7-acetic acid (1.84 g, 11 mmol) and the product resulting from Example 15 (2.42 g, 10.0 mmol) were treated as described in Example 19. Purification and conversion to the dihydrichloride salt yielded 0.91 g of the desired product as a white solid. m.p. 87-90 °C. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 1.8 (m, 4H), 2.4-2.7 (m, 2H), 3.0 (s, 3H), 3.2-3.8 (m, 7H), 3.8 (s, 3H), 6.8 (d, 1H), 6.9 (d, 1H), 7.15 (t, 1H), 7.9 (m, 2H), 8.2 (m, 2H), 8.95 (d, 1H), 9.17 (d, 1H). Anal calcd for $C_{24}H_{30}Cl_2N_2O \cdot 0.75\ H_2O$: C, 64.49; H, 7.10; N, 6.27. Found: C, 64.42; H, 6.84; N, 6.12.

Example 41

N-[2-(Isoquinolin-6-yl)ethyl]-N-[(R)-5-methoxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]-N-methylamine methanesulfonate

Isoquinoline-6-acetic acid and the product resulting from Example 15 are treated by the procedure described in Example 19 to yield the title compound.

Example 42

N-[2-(Isoquinolin-7-yl)ethyl]-N-[(R)-5-methoxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]-N-methylamine methanesulfonate

Isoqunioline-7-acetic acid and the product resulting from Example 15 are treated by the procedure described in Example 19 to yield the title compound.

Example 43

N-[2-(N-Methanesulfonamido-2,3-dihydroindol-6-yl)ethyl]-N-[(R)-5-methoxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]-N-methylamine methanesulfonate

N-Methanesulfonamido-2,3-dihydroindole-6-acetic acid and the product resulting from Example 15 are treated by the procedure described in Example 19 to yield the title compound.

Example 44

N-[2-(N-Methyl-2,3-dihydroindol-6-yl)ethyl]-N-[(R)-5-methoxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]-N-methylamine methanesulfonate

N-Methyl-2,3-dihydroindole-6-acetic acid and the product resulting from Example 15 are treated by the procedure described in Example 19 to yield the title compound.

Example 45

N-[2-(2,3-Dihydroindol-6-yl)ethyl-N-[(R)-5-methoxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]-N-methylamine dihydrochloride

The compound resulting from Example 15 (800 mg, 3.3 mmol) was reacted with (2-indolinone-6-yl)acetic acid (700 mg, 3.7 mmol) by the procedure described in Example 77A to give N-(2-indolinone-6-yl)acetyl-N-[(R)-5-methoxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]-N-methylamine (1.17 g). This acetamido compound (1.00 g, 2.64 mmol) was refluxed in THF (20 mL) with 1 M diborane in THF (21 mL, 21 mmol) for 4 hours, cooled and carefully quenched with methanol. The solvent was removed under reduced pressure, and methanol and hydrogen

chloride in isopropanol was added. The mixture was refluxed for 2 hours and then stirred overnight at ambient temperature. The solvent was removed under reduced pressure and the salt was converted to its free base with dilute sodium hydroxide. The mixture was extracted three times with ethyl acetate and the combined organic extracts were washed with brine, dried, and concentrated *in vacuo*. The residue obtained was chromatographed on silica gel eluting with 2:8 hexane-ethyl acetate to give 310 mg of the free base. The free base was dissolved in ethyl acetate containing ethanol and then treated with hydrogen chloride in isopropanol followed by ether. The dihydrochloride salt crystallized from solution to give 360 mg of the title compound. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.50-2.25 (m, 8H), 2.50 (m, 4H), 2.76 (m, 4H), 2.99 (t, 2H), 3.54 (t, 2H), 3.81 (m, 3H), 6.54 (m, 1.5H), 6.68 (m, 1H), 6.80 (m, 1H), 7.05 (m, 1.5H). MS (DCI/NH_3) m/e 351 $(M+H)^+$. Anal calcd for $C_{23}H_{30}N_2O \cdot 2HCl \cdot 0.5\ H_2O$: C, 63.88; H, 7.69; N, 6.48. Found: C, 63.45; H, 7.53; N, 6.39.

Example 46

N-[2-(2,3-Dihydroindol-5-yl)ethyl]-N-[(R)-5-methoxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]-N-methylamine methanesulfonate

2,3-Dihydroindole-5-acetic acid and the product resulting from Example 15 are treated by the procedure described in Example 19 to yield the title compound.

Example 47

N-[2-(Indol-6-yl)ethyl]-N-[(R)-5-methoxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]-N-methylamine fumarate 3/4 hydrate

Indole-6-acetic acid (0.69 g) and the product resulting from Example 15 (0.70 g) were treated by the procedure described in Example 19, substituting lithium aluminum hydride for borane, to yield 0.49 g of the desired product as a white powder. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 1.6-3.0 (m, 13H), 2.99 (d, 3H), 3.73 (s, 3H), 6.60 (s, 1H), 6.72 (d, 1H), 6.76 (d, 1H), 6.86 (d, 1H), 7.05 (t, 1H), 7.22 (m, 2H), 7.41 (d, 1H), 10.95 (bs, 1H). Anal calcd for $C_{27}H_{32}N_2O_5 \cdot 0.75H_2O$: C, 67.83; H, 7.06; N, 5.70. Found: C, 67.97; H, 6.97; N, 5.70.

Example 48

N-[2-(N-Methanesulfondamido-1,3-dihydroisoindol-5-yl)ethyl]-N-[(R)-5-methoxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]-N-methylamine methanesulfonate hemihydrate

N-Methanesulfonamido-1,3-dihydroisoindole-5-acetic acid (1.0 g) and the product resulting from Example 15 (1.05 g) were treated by the procedure described in Example 19 to yield 0.77 g of the desired product as a white solid. m.p. 209 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) of the free base δ 1.5-2.0 (m, 6H), 2.38 (s, 3H), 2.4-3.0 (m, 7H), 2.88 (s, 3H), 3.81 (s, 3H), 4.68 (s, 4H), 6.67 (d, 1H), 6.80 (d, 1H), 7.1 (m, 4H). Anal calcd for $C_{25}H_{36}N_2O_6S_2 \cdot 0.5H_2O$: C, 56.26; H, 6.99; N, 5.25. Found: C, 55.85; H, 6.78; N, 5.24.

Example 49

N-[2-(N-Methyl-1,3-dihydroisoindol-5-yl)ethyl]-N-[(R)-5-methoxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]-N-methylamine dihydrochloride

The compound resulting from Example 50 (288 mg, 0.68 mmol) was dissolved in methanol (10 mL) and formaldehyde (3 mL) was added followed by sodium cyanoborohydride (427 mg, 6.8 mmol). The reaction was stirred at ambient temperature for 45 minutes and then quenched with 1 N sodium hydroxide solution. The mixture was extracted and the organic solution was washed with brine, dried and concentrated *in vacuo*. The residue obtained was dissolved in ethyl acetate containing ethanol and treated with an isopropyl alcohol solution of hydrogen chloride. Ether was added and the desired compound crystallized from solution to give 230 mg. Recrystallization from ethanol-ether afforded 170 mg of the title compound. m.p. 270 °C. The 300 MHz ^{1}H NMR spectrum was found to be consistent with the desired product. MS (DCI/NH_3) m/e 365 $(M+H)^+$. Anal calcd for $C_{24}H_{32}N_2O \cdot 2HCl \cdot 0.5\ H_2O$: C, 64.57; H, 7.90; N, 6.27. Found: C, 64.59; H, 7.82; N, 6.19.

Example 50

N-[2-(1,3-Dihydroisoindol-5-yl)ethyl]-N-[(R)-5-methoxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]-N-methylamine dihydrochloride

Step A

N-[2-(N-Benzoyl-1,3-dihydroisoindol-5-yl)ethyl]-N-[(R)-5-methoxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]-N-methylamine

N-[(R)-5-Methoxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]-N-methylamine hydrochloride, resulting from Example 15 (1.55 g, 6.4 mmol), N-benzoyl-1,3-dihydroisoindol-5-yl acetic acid (2.00 g, 7.1 mmol), 1-hydroxybenzotriazole (1.3 g, 9.6 mmol), 1-(3-dimethylaminopropyl-3-ethylcarbodiimide hydrochloride (EDCI) (1.5 g, 7.7 mmol) and triethylamine (0.72 g, 7.1 mmol) were dissolved in tetrahydrofuran (80 mL) and stirred at ambient temperature for 3 hours. The solution was poured into ice/water and extracted with ethyl acetate (3x); the organic phase was washed with 1 N sodium hydroxide solution, 1 N hydrochloric acid, and brine, dried and concentrated under reduced pressure to afford 2.74 g (88%) of the title compound.

Step B

N-[2-(N-Benzyl-1,3-dihydroisoindol-5-yl)ethyl]-N-[(R)-5-methoxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]-N-methylamine hydrochloride

The compound resulting from Example Step A (2.74 g, 5.8 mmol) and diborane (1 M solution in THF) (47 mL, 46.8 mmol) in THF (30 mL) were stirred at ambient temperature overnight. The reaction mixture was heated at reflux for 1 hour and then cooled and carefully quenched with methanol. The volatiles were removed under reduced pressure and methanol was added followed by a solution of hydrogen chloride in isopropyl alcohol. The reaction mixture was refluxed for 1.5 hours and the solvent removed under reduced pressure. The residue obtained was dissolved in boiling ethyl acetate and allowed to stand at ambient temperature for 2 days. The title compound crystallized from solution to give 2.62 g (92%).

Step C

N-[2-(1,3-Dihydroisoindol-5-yl)ethyl]-N-[(R)-5-methoxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]-N-methylamine dihydrochloride

The compound resulting from Step B was catalytically hydrogenated. The catalyst was removed by filtration and the filtrate concentrated *in vacuo*. The residue obtained was triturated with ether to give 830 mg (93%) of the title compound. ^{1}H NMR (CD_3OD, 300 MHz) δ 1.88 (m, 5H), 3.05-3.30 (m, 5H), 3.45 (m, 5H), 3.80 (s, 3H), 4.62 (m, 4H), 6.83 (m, 2H), 7.16 (t, 1H), 7.40 (m, 3H). MS (DCI/NH_3) m/e 352 $(M+H)^+$. Anal calcd for $C_{23}H_{30}N_2O \cdot 2HCl \cdot 0.5\ H_2O$: C, 63.88; H, 7.69; N, 6.48. Found: C, 63.79; H, 7.49; N, 6.33.

Example 51

N-[2-(Benzothiazol-6-yl)ethyl]-N-[(R)-5-methoxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]-N-methylamine methanesulfonate

Benzothiazole-6-acetic acid (0.95 g) and the product resulting from Example 15 (0.90 g) were treated by the procedure described in Example 19, substituting 4 equivalents of TMEDA (N,N,N',N'-tetramethylethylenediamine) for the hydrochloric acid treatment to decompose the intermediate borane complex, to yield 0.67 g of the desired product as a white solid. m.p. 165-167 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) of the free base δ 1.4-2.0 (m, 6H), 2.47 (s, 3H), 2.4-3.1 (m, 7H), 3.80 (s, 3H), 6.67 (d, 1H), 6.80 (d, 1H), 7.09 (t, 1H), 7.35 (m, 2H), 7.80 (s, 1H), 8.04 (d, 1H), 8.91 (s, 1H). Anal calcd for $C_{23}H_{30}N_2O_4S_2$: C, 59.71; H, 6.54; N, 6.05. Found: C, 59.25; H, 6.48; N, 5.96.

Example 52

N-[2-(2-Chlorobenzothiazol-5-yl)ethyl]-N-[(R)-5-methoxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]-N-methylamine methanesulfonate

2-Chlorobenzothiazole-5-acetic acid and the product resulting from Example 15 are treated by the procedure described in Example 37 to yield the title compound.

Example 53

N-[2-(2-Benzothiazol-5-yl)ethyl]-N-[(R)-5-methoxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]-N-methylamine methanesulfonate

Benzothiazole-5-acetic acid and the product resulting from Example 15 are treated by the procedure described in Example 51 to yield the title compound.

Example 54

N-[2-(2,3-Dihydro-benzo[b]thien-6-yl)ethyl]-N-[(R)-5-methoxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]-N-methylamine methanesulfonate

2,3-Dihydrobenzo[b]thiophene-6-acetic acid and the product from Example 15 are treated according to the method of Example 19.

Example 55

N-[2-(1-Oxo-2,3-dihydrobenzo[b]thien-5-yl)ethyl]-N-[(R)-5-methoxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]-N-methylamine methanesulfonate

The product resulting from Example 26 is treated with one equivalent of *m*-chloroperbenzoic acid to yield the title compound.

Example 56

N-[2-(1,1-Dioxo-2,3-dihydrobenzo[b]thiophen-5-yl)ethyl]-N-[(R)-5-methoxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]-N-methylamine hydrochloride

5-(2-Bromoethyl)-1,1-dioxo-2,3-dihydrobenzothiophene (0.315 g, 1.15 mmol) and the product resulting from Example 15 (0.332 g, 1.38 mmol) were combined with diisopropylethyl amine (0.50 ml, 2.8 mmol) in acetonitrile (3 mL). After 6 hours at 75 °C., the product was isolated, purified and converted to its hydrochloride salt to yield 0.147 g of the desired product as a white solid. m.p. 225-226 °C. ^{1}H NMR (CD_3OD, 300 MHz) δ 1.8-2.0 (m, 4H), 2.5-2.9 (m, 2H), 3.0-3.6 (m, 14H), 3.81 (s, 3H), 6.8 (m, 2H), 7.15 (t, 1H), 7.4-7.5 (m, 2H), 7.7 (m, 1H). Anal calcd for $C_{23}H_{30}ClNO_3S$: C, 63.36; H, 6.94; N, 3.21. Found: C, 63.18; H, 6.90; N, 3.10.

Example 57

N-[2-(1-Oxo-2,3-dihydrobenzo[b]thien-6-yl)ethyl]-N-[(R)-5-methoxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]-N-methylamine methanesulfonate

The product resulting from Example 54 is treated with one equivalent of *m*-chloroperbenzoic acid to yield the title compound.

Example 58

N-[2-(1,3-Dihydro-isobenzofuran-5-yl)-ethyl]-N-[(R)-5-methoxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]-N-methylamine methanesulfonate

1,3-Dihydroisobenzofuran-5-acetic acid (1.00 g) and the product resulting from Example 15 (0.95 g) were treated by the procedure described in Example 19, substituting lithium aluminum hydride for borane, to yield 0.77 g of the desired

product as a white solid. m.p. 162-164 °C. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 1.6-2.0 (m, 4H), 2.99 (d, 3H), 2.5-3.5 (m, 9H), 3.73 (s, 3H), 5.0 (m, 4H), 6.8-7.3 (m, 6H). Anal calcd for $C_{24}H_{33}NO_5S$: C, 64.40; H, 7.43; N, 3.13. Found: C, 64.35; H, 7.43; N, 3.13.

Example 59

N-[2-(Benzo[1,3]oxathiol-5-yl)ethyl]-N-[(R)-5-methoxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]-N-methylamine methanesulfonate

Benzo[1,3]oxathiol-5-acetic acid and the product resulting from Example 15 are treated by the procedure described in Example 19 to yield the title compound.

Example 60

N-[2-(Benzo[1,3]oxathiol-6-yl)ethyl]-N-[(R)-5-methoxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]-N-methylamine methanesulfonate

Benzo[1,3]oxathiol-6-acetic acid and the product resulting from Example 15 are treated by the procedure described in Example 19 to yield the title compound.

Example 61

N-[2-(2-Amino-benzothiazol-5-yl)-ethyl]-N-[(R)-5-methoxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]-N-methylamine bis-methanesulfonate

2-Amino-benzothiazole-5-acetic acid (1.15 g) and the product resulting from Example 15 (1.30 g) were treated by the procedure described in Example 19, substituting 4 equivalents of TMEDA (N,N,N',N'-tetramethylethylenediamine) for the hydrochloric acid treatment to decompose the intermediate borane complex, to yield 0.97 g of the desired product as a white solid. m.p. 200-202 °C. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 1.4-2.0 (m, 6H), 2.47 (s, 3H), 2.4-3.0 (m, 7H), 3.81 (s, 3H), 5.1 (bs, 2H), 6.65 (d, 1H), 6.80 (d, 1H), 7.09 (t, 1H), 7.14 (dd, 1H), 7.44 (bs, 1H), 7.47 (d, 1H). Anal calcd for $C_{24}H_{35}N_3O_7S_3$: C, 50.24; H, 6.15; N, 7.32. Found: C, 50.62; H, 6.07; N, 7.31.

Example 62

N-[(2-Benzofuran-5-yl)-ethyl]-N-[(R)-5-methoxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]-N-methylamine methanesulfonate

Benzofuran-5-acetic acid (0.53 g) and the product resulting from Example 15 (0.85 g) were treated by the procedure described in Example 19, substituting

lithium aluminum hydride for borane, to yield 0.85 g of the desired product as a white solid. m.p. 169-171 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) of the free base δ 1.6-2.0 (m, 5H), 2.40 (s, 3H), 2.4-3.0 (m, 8H), 3.81 (s, 3H), 6.67 (d, 1H), 6.70 (dd, 1H), 6.80 (d, 1H), 7.09 (t, 1H), 7.12 (dd, 1H), 7.40 (d, 1H), 7.41 (s, 1H), 7.59 (d, 1H). Anal calcd for $C_{24}H_{31}NO_5S$: C, 64.70; H, 7.01; N, 3.14. Found: C, 65.01; H, 7.14; N, 3.19.

Example 63

N-[2-(N-Methyl-2,3-dihydro-1H-indol-5-yl)-ethyl]-N-[(R)-5-methoxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]-N-methylamine bis-methanesulfonate

1-Methyl-2,3-dihydroindole-5-acetic acid (0.70 g), and the product resulting from Example 15 (0.95 g) were treated by the procedure described in Example 19 to yield 0.88 g of the desired product as a white solid. m.p. 189-190 °C. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 1.6-1.9 (m, 5H), 2.4-3.7 (m, 12H), 2.75 (s, 3H), 2.95 (d, 3H), 3.77 (s, 3H), 6.6-7.2 (m, 6H), 9.0 (bs, 1H). Anal calcd for $C_{26}H_{40}N_2O_7S_2$: C, 56.09; H, 7.24; N, 5.03. Found: C, 56.22; H, 7.59; N, 4.95.

Example 64

5-{2-[((R)-5-Methoxy-1,2,3,4-tetrahydro-naphthalen-1-ylmethyl)methyl-amino]-ethyl}-1,3-dihydro-indol-2-one methanesulfonate mono-hydrate

5-(2-Chloroethyl)-2,3-dihydroindol-2-one (1.4 g) and the product resulting from Example 15 (1.2 g) were combined in dimethylformamide with sodium carbonate (1.10 g), ethyldiisopropyl amine (1.0 ml), and sodium iodide (5 mg) and heated at 100 °C. for 18 hours. After chromatographic purification and conversion to its methanesulfonate salt, the desired product (0.44 g) was obtained as a white solid. m.p. 133-134 °C. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 1.6-2.0 (m, 5H), 2.4-3.5 (m, 8H), 2.31 (s, 3H), 2.97 (d, 3H), 3.48 (s, 2H), 3.78 (s, 3H), 6.7-7.2 (m, 6H), 9.1 (bs, 1H), 9.87 (s, 1H). Anal calcd for $C_{24}H_{32}N_2O_5S \cdot H_2O$: C, 60.23; H, 7.16; N, 5.85. Found: C, 59.95; H, 6.81; N, 5.78.

Example 65

6-{2-[((R)-5-Methoxy-1,2,3,4-tetrahydro-naphthalen-1-ylmethyl)methyl-amino]-ethyl}-3H-benzoxazol-2-one hydrochloride

4-Nitro-3-hydroxyphenylacetic acid (0.91 g) and the product resulting from Example 15 (1.0 g) were treated by the procedure described in Example 19. The intermediate product was treated with H_2/Pd in EtOH to yield the intermediate amino-phenol. Treatment of this intermediate with 1,1'-carbonyldiimidazole in THF at reflux for 2 hours, followed by isolation and conversion to the hydrochloride salt yielded 0.49 g of the desired product as a white solid. m.p. 147-149 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) of the free base δ 1.55-2.0 (m, 4H), 2.39 (s, 3H), 2.4-3.0 (m, 9H), 3.81 (s, 3H), 6.67 (d, 1H), 6.80 (d, 1H), 6.97 (m, 2H), 7.1 (m, 2H), 8.7 (bs, 1H). Anal calcd for $C_{22}H_{27}ClN_2O_3$: C, 65.58; H, 6.75; N, 6.95. Found: C, 65.18; H, 6.86; N, 6.97.

Example 66

5-{2-[((R)-5-Methoxy-1,2,3,4-tetrahydro-naphthalen-1-ylmethyl)methyl-amino]-ethyl}-3H-imidazol-2-one hydrochloride hydrate

4-Amino-3-nitrophenylacetic acid (1.34 g) and the product resulting from Example 15 (1.50 g) were treated by the procedure described in Example 19. The intermediate product was treated with H_2/Pd in EtOH to yield the intermediate di-aniline. Treatment of this intermediate with 1,1'-carbonyldiimidazole in THF at reflux for 2 hours, followed by isolation and conversion to the hydrochloride salt yielded 0.33 g of the desired product as a white solid. m.p. 192-196 °C. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 1.6-1.9 (m, 4H), 2.4-3.5 (m, 9H), 2.9 (d, 3H), 3.77 (s, 3H), 6.85 (m, 5H), 7.12 (t, 1H), 9.8 (bs, 1H), 10.08 (s, 1H), 10.17 (s, 1H). Anal calcd for $C_{22}H_{28}ClN_3O_2 \cdot 0.75H_2O$: C, 63.60; H, 7.16; N, 10.11. Found: C, 63.70; H, 6.90; N, 9.94.

Example 67

N-[2-(Benzo[b]thien-5-yl)ethyl]-N-[(R)-5-methoxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]-N-methylamine methanesulfonate

Benzothiophene-5-acetic acid (0.90 g) and the product resulting from Example 15 (1.03 g) were treated by the procedure described in Example 19. The intermediate amide was treated with lithium aluminum hydride and following isolation and conversion to the methanesulfonate salt yielded 0.95 g of the desired product as a white solid. m.p. 181-182 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.75-

2.25 (m, 5H), 2.55 (m, 1H), 2.78 (m, 1H), 2.88 (s, 3H), 3.04 (d, 3H), 3.20-3.65 (m, 6H), 3.81 (s, 3H), 6.70 (m, 2H), 7.13 (t, 1H), 7.30 (m, 2H), 7.47 (d, 1H), 7.73 (d, 1H), 7.82 (d, 1H), 11.0 (bs, 1H). Anal calcd for $C_{24}H_{31}NO_4S_2$: C, 62.44; H, 6.77; N, 3.03. Found: C, 62.32; H, 6.71; N, 3.01.

Example 68

N-[2-(Benzo[b]thien-6-yl)ethyl]-N-[(R)-5-methoxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]-N-methylamine methanesulfonate

Benzothiophene-6-acetic acid (0.84 g) and the product resulting from Example 15 (0.96 g) were treated by the procedure described in Example 19. The intermediate amide was treated with lithium aluminum hydride and following isolation and conversion to the methanesulfonate salt yielded 0.80 g of the desired product as a white solid. m.p. 198-199 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.75-2.25 (m, 5H), 2.55 (m, 1H), 2.78 (m, 1H), 2.88 (s, 3H), 3.04 (d, 3H), 3.20-3.65 (m, 6H), 3.81 (s, 3H), 6.72 (m, 2H), 7.15 (t, 1H), 7.30 (m, 2H), 7.47 (d, 1H), 7.80 (m, 2H), 11.0 (bs, 1H). Anal calcd for $C_{24}H_{31}NO_4S_2$: C, 62.44; H, 6.77; N, 3.03. Found: C, 62.24; H, 6.67; N, 3.09.

Example 69

5-{2-[((R)-5-Methoxy-1,2,3,4-tetrahydro-naphthalen-1-ylmethyl)methyl-amino]-ethyl}-3H-benzoxazol-2-one hydrochloride

3-Nitro-4-hydroxyphenylacetic acid (1.47 g) and the product resulting from Example 15 (1.50 g) were treated by the procedure described in Example 19. The intermediate product was treated with H_2/Pd in EtOH to yield the intermediate amino-phenol. Treatment of this intermediate with 1,1'-carbonyldiimidazole in THF at reflux for 2 hours, followed by isolation and conversion to the hydrochloride salt yielded 0.80 g of the desired product as a white solid. m.p. 115-119 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.7-2.1 (m, 4H), 2.15-2.4 (m, 1H), 2.42-2.59 (m, 1H), 2.67-2.81 (m, 1H), 3.02 (d, 3H), 3.1-3.6 (m, 6H), 3.80 (s, 3H), 6.69 (d, 1H), 6.73-7.0 (m, 3H), 7.13 (t, 1H), 7.22 (d, 1H), 10.49 (s, 1H), 11.4 (bs, 1H). Anal calcd for $C_{22}H_{27}ClN_2O_3$: C, 65.58; H, 6.75; N, 6.95. Found: C, 65.16; H, 6.75; N, 6.77.

Example 70

N-[2-(6-Methyl-2,3-dihydro-benzofuran-5-yl)ethyl]-N-[(R)-5-methoxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]-N-methylamine methanesulfonate

6-Methyl-2,3-dihydrobenzofuran-5-acetic acid (0.63 g) and the product resulting from Example 15 (0.72 g) were treated by the procedure described in Example 19 to yield 0.60 g of the desired product as a white solid. m.p. 199-200 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) of the free base δ 1.6-2.0 (m, 4H), 2.26 (s, 3H), 2.40 (s, 3H), 2.4-3.0 (m, 9H), 3.14 (t, 2H), 3.81 (s, 3H), 4.51 (t, 2H), 6.59 (s, 1H), 6.67 (d, 1H), 6.81 (d, 1H), 6.97 (s, 1H), 7.09 (t, 1H). Anal calcd for $C_{25}H_{35}NO_5S$: C, 65.05; H, 7.64; N, 3.03. Found: C, 65.08; H, 7.62; N, 3.09.

Example 71

N-[2-(2-Methyl-benzoxazol-6-yl)ethyl]-N-[(R)-5-methoxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]-N-methylamine methanesulfonate

4-Nitro-3-hydroxyphenylacetic acid (1.70 g) and the product resulting from Example 15 (2.00 g) were treated by the procedure described in Example 19. The intermediate product was treated with hydrogen over a palladium catalyst in EtOH to yield the intermediate amino-phenol, which was dissolved in triethyl orthoacetate and heated at reflux for 1 hour. This intermediate was then treated with methanesulfonic acid to yield 1.15 g of the desired product as a white solid. m.p. 159-161 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) of the free base δ 1.6-2.0 (m, 5H), 2.39 (s, 3H), 2.4-3.0 (m, 8H), 2.61 (s, 3H), 3.80 (s, 3H), 6.66 (d, 1H), 6.80 (d, 1H), 7.08 (d, 1H), 7.12 (dd, 1H), 7.31 (d, 1H), 7.52 (d, 1H). Anal calcd for $C_{24}H_{32}N_2O_5S$: C, 62.59; H, 7.00; N, 6.08. Found: C, 62.59; H, 6.96; N, 6.11.

Example 72

N-[2-(2-Methyl-benzoxazol-5-yl)ethyl]-N-[(R)-5-methoxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]-N-methylamine methanesulfonate

3-Nitro-4-hydroxyphenylacetic acid (1.70 g) and the product resulting from Example 15 (2.00 g) were treated by the procedure described in Example 19. The intermediate product was treated with hydrogen over a palladium catalyst in EtOH to yield the intermediate amino-phenol, which was dissolved in triethyl orthoacetate and heated at reflux for 1 hour. This intermediate was then treated with methanesulfonic acid to yield 1.36 g of the desired product as a white solid. m.p. 178-179 °C. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 1.7-1.9 (m, 4H), 2.31 (s, 3H), 2.60 (s, 3H), 2.96 (d, 3H), 2.9-3.6 (m, 9H), 3.79 (s, 3H), 6.81 (d, 1H), 6.89 (d, 1H), 7.16 (t, 1H), 7.29 (dd, 1H), 7.65 (m, 2H), 9.2 (bs, 1H). Anal calcd for

$C_{24}H_{32}N_2O_5S$: C, 62.59; H, 7.00; N, 6.08. Found: C, 62.64; H, 6.96; N, 6.10.

Example 73

N-[2-(2-Propanesulfonyl-2,3-dihydro-1H-isoindol-5-yl)ethyl]-N-[(R)-5-methoxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]-N-methylamine hydrochloride

2-Propanesulfonyl-2,3-dihydro-1H-isoindole-5-acetic acid (0.75 g) and the product resulting from Example 15 (0.57 g) were treated by the procedure described in Example 19 to yield 0.435 g of the desired product as a white solid. m.p. 197-198 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) of the free base δ 1.05 (t, 3H), 1.6-2.0 (m, 6H), 2.47 (s, 3H), 2.4-3.0 (m, 9H), 3.00 (m, 2H), 3.80 (s, 3H), 4.69 (s, 4H), 6.66 (d, 1H), 6.80 (d, 1H), 7.1 (m, 4H). Anal calcd for $C_{26}H_{37}ClN_2O_3S$: C, 63.33; H, 7.56; N, 5.68. Found: C, 63.12; H, 7.54; N, 5.63.

Example 74

N-[2-(1,1-Dioxo-2,3-dihydrobenzothiophen-6-yl)ethyl]-N-[(R)-5-methoxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]-N-methylamine methanesulfonate

The product resulting from Example 54 is treated with two equivalents of *m*-chloroperbenzoic acid to yield the title compound.

Example 75

N-[2-(N-Trifluoromethanesulfonamido-1,3-dihydroisoindol-5-yl)ethyl]-N-[(R)-5-methoxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]-N-methylamine methanesulfonate

The compound resulting from Example 50 as its free base (340 mg, 1 mmol) was dissolved in methylene chloride (10 mL) and treated with triethylamine (0.68 mL, 5 mmol) and trifluoromethanesulfonic anhydride (0.85 g, 3 mmol) by the procedure described in Example 15 to give crude material. Chromatography on silica gel eluting with 3:7 ethyl acetate-hexane afforded 200 mg of material which was rechromatographed using the same conditions to give 158 mg of the trifluoromethanesulfonyl compound. The free base (152 mg, 0.315 mmol) was dissolved in ethyl acetate and methanesulfonic acid (0.23 mL, 0.346 mmol) in isopropyl alcohol was added dropwise. The desired salt crystallized from solution and was filtered and dried to give 158 mg of the title compound. m.p. 210 °C. The 300 MHz ^{1}H NMR spectrum was found to be consistent with the desired product.

MS (DCI/NH_3) m/e 483 $(M+H)^+$. Anal calcd for $C_{24}H_{29}N_2F_3O_3S$: C, 51.98; H, 5.75; N, 4.84. Found: C. 51.77; H, 5.80; N, 4.80.

Example 76

N-[2-(N-Ethanesulfonamido-1,3-dihydroisoindol-5-yl)ethyl]-N-[(R)-5-methoxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]-N-methylamine methanesulfonate

Step A

N-[(N-Ethanesulfonamido-1,3-dihydroisoindol-5-yl)acetyl]-N-[(R)-5-methoxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]-N-methylamine methanesulfonate

N-[(R)-5-Methoxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]-N-methylamine hydrochloride, resulting from Example 15 (484 mg, 2mmol) was reacted with N-[2-(N-ethanesulfonamido-1,3-dihydroisoindol-5-yl)acetic acid (600 mg, 2.2 mmol) by the procedure described in Example 50, Step A to give crude material. Column chromatography on silica gel eluting with 1:1 ethyl acetate-hexane followed by ethyl acetate afforded the title compound 790 mg (87%).

Step B

N-[2-(N-Ethanesulfonamido-1,3-dihydroisoindol-5-yl)ethyl-N-[(R)-5-methoxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]-N-methylamine methanesulfonate

The compound resulting from Step A (790 mg, 1.7 mmol) was dissolved in THF (20 mL), treated with 1 M diborane in THF (7 mL, 6.9 mmol) and then heated at reflux for 2.5 hours. The solvent was removed under reduced pressure and methanol was added to the residue followed by an isopropyl alcohol solution of hydrogen chloride (10 mL). The reaction mixture was heated at reflux for 1.5 hours, the solvent was removed under reduced pressure and an aqueous solution of potassium hydroxide was added. The mixture was extracted with ethyl acetate (3x), washed with brine, dried and concentrated under reduced pressure to afford an oil. Chromatography on silica gel eluting with 1:1 ethyl acetate-hexane followed by ethyl acetate followed by hydrochloride salt formation afforded the title compound (530 mg, 71%) as its hydrochloride salt. The salt was converted to its free base (530 mg, 1.2 mmol) and then dissolved in ethyl acetate containing ethanol. Methanesulfonic acid (0.09 mL, 1.4 mmol) in isopropanol was added followed by ether. The desired product crystallized from solution. m.p. 181-182 °C. The 300 MHz ^1H NMR

MHz ^{1}H NMR spectrum was found to be consistent with the desired product. MS (DCI/NH_3) m/e 443 $(M+H)^+$. Anal calcd for $C_{25}H_{34}N_2O_3S \cdot CH_3SO_3H \cdot 0.25$ H_2O: C, 57.49; H, 7.14; N, 5.16. Found: C, 57.21; H, 6.90; N, 5.14.

Example 77

N-[2-(Benzofuran-7-yl)ethyl-N-[(R)-8-fluoro-5-methoxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]-N-methylamine methanesulfonate

Benzo[b]furan-7-acetic acid and the compound resulting from Example 16 (590 mg, 1.5 mmol) were treated as described in Example 19, substituting final HCl treatment with TMEDA (N,N,N',N'-tetramethylethylenediamine) (2.79 g, 24 mmol). The reaction mixture was stirred for two hours at ambient temperature and then quenched with sodium bicarbonate solution and extracted with ethyl acetate. The combined organic extracts were washed with brine, dried and concentrated *in vacuo* to afford crude product (660 mg). Column chromatography on silica gel eluting with 2:8 ethyl acetate-hexane afforded 400 mg (73%) of the title compound free base. The free base in ethyl acetate was treated with 0.08 mL of methanesulfonic acid in isopropanol to afford the title compound. m.p. 121-122 °C. The 300 MHz ^{1}H NMR spectrum was found to be consistent with the desired product. Anal calcd for $C_{23}H_{26}FNO_2$: C, 62.18; H, 6.52; N, 3.02. Found: C, 61.77; H, 6.54; N, 2.98.

Example 78

N-[2-(Benzofuran-6-yl)ethyl-N-[(R)-8-fluoro-5-methoxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]-N-methylamine methanesulfonate

The product resulting from Example 16 (484 mg, 2mmol) was reacted with (benzofuran-6-yl)acetic acid (0.49 g, 2.8 mmol) by the procedure described in Example 77A to give N-[2-(benzofuran-6-yl)acetyl-N-[(R)-8-fluoro-5-methoxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]-N-methylamine which was chromatographed on silica gel eluting with 3:7 ethyl acetate-hexane to give 810 mg (92%) of pure material.

The above carboxamide (810 mg, 2.1 mmol) was reduced using BH_3•THF followed by TMEDA treatment as described in Example 77 to give 600 mg (78%) of the free base which was converted into 630 mg of the title compound. m.p. 159-160 °C. The 300 MHz ^{1}H NMR spectrum was found to be consistent with the desired product. MS (DCI/NH_3) m/e 368 $(M+H)^+$. Anal calcd for $C_{23}H_{26}FNO_2$ $\cdot CH_3SO_3H$: C, 62.18; H, 6.52; N, 3.02. Found: C, 62.09; H, 6.49; N, 3.02.

Example 79

N-[2-(2,3-Dihydrobenzofuran-6-yl)ethyl-N-[(R)-5-hydroxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]-amine hydrochloride

Step A

N-[(R)-5-Hydroxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]amine

To N-[(R)-5-methoxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]amine (1.00 g, 4.39 mmol) dissolved in methylene chloride (30 mL) and cooled to -70 °C was added boron tribromide (1.7 mL, 17.6 mmol) dropwise. The cooling bath was removed and the reaction mixture stirred at ambient temperature for 4 hours. The reaction mixture was cooled in an ice bath and 15 mL of methanol was added dropwise followed by ether. The reaction mixture was stirred overnight at ambient temperature and then concentrated *in vacuo* and chased with methanol. The resulting solid was slurried in ether and filtered to give the title compound.

Step B

N-[2-(2,3-Dihydrobenzofuran-6-yl)ethyl-N-[(R)-5-hydroxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]-amine hydrochloride

The compound resulting from Step A (201 mg, 0.78 mmol) was reacted with 2,3-dihydrobenzofuran-6-ylacetic acid (172 mg, 0.97 mmol) by the procedure described in Example 50A to give the carboxamido compound (130 mg). This compound (130 mg) was reduced with diborane by the procedure described in Example 79 to give the title compound, which was recrystallized from ethanol and ether to give 102 mg. m.p. 227-228 °C. The 300 MHz ^{1}H NMR spectrum was found to be consistent with the desired product. MS (DCI/NH_3) m/e 324 $(M+H)^+$.

Example 80

N-[2-(2-Indolinone-6-yl)ethyl-N-[(R)-5-methoxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]-N-methylamine methanesulfonate

The compound resulting from Example 15 (0.85 g, 3.5 mmol) was converted to its free base and then reacted with 2-(2-indolinone-6-yl)ethyl bromide (0.94 g, 3.9 mmol) in acetonitrile and diisopropylethylamine (0.73 mL, 4.2 mmol) at reflux for 3 hours and at ambient temperature overnight. The reaction mixture was refluxed for an additional hour and then concentrated *in vacuo*. The residue obtained was dissolved in methylene chloride, washed with sodium bicarbonate and

brine, dried and concentrated under reduced pressure. The residue obtained was chromatographed on silica gel eluting with 1:1 ethyl acetate-hexane followed by 80% ethyl acetate in hexane to afford 750 mg (69%) of the title compound free base. The free base was dissolved in ethyl acetate containing ethanol and treated with methanesulfonic acid (0.16 mL, 2.5 mmol) followed by isopropyl alcohol. Upon addition of ether, the methanesulfonate salt crystallized from solution to give 700 mg of the title compound. m.p. 168-169 °C. The 300 MHz ^{1}H NMR spectrum was found to be consistent with the desired product. MS (DCI/NH_3) m/e 365 $(M+H)^+$. Anal calcd for $C_{23}H_{28}N_2O_2 \cdot CH_3SO_3H$: C, 62.59; H, 7.00; N, 6.08. Found: C, 62.36; H, 6.94; N, 5.99.

Example 81

N-[2-(N-Methanesulfonamido-1,3-dihydroisoindol-5-yl)ethyl-N-[(R)-5,6-methylenedioxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]-N-ethylamine hydrochloride

N-[2-(N-Methanesulfonamido-1,3-dihydroisoindol-5-yl)acetyl-N-[(R)-5,6-methylenedioxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]-N-ethylamine was prepared by the procedure described in Example 50A from N-methanesulfonamido-1,3-dihydroisoindol-5-yl)acetic acid (940 mg, 3.7 mmol) and N-[(R)-5,6-methylenedioxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]-N-ethylamine, prepared by the procedure described in Example 112, (900 mg, 3.3 mmol). This acetamido compound (1.00 g, 2.1 mmol) was reduced with diborane by the procedure described in Example 79 to give 620 mg of the free base. This purified material was converted to a hydrochloride salt (460 mg). m.p. 90-100 °C. The 300 MHz ^{1}H NMR spectrum was found to be consistent with the desired product. MS (DCI/NH_3) m/e 457 $(M+H)^+$. Anal calcd for $C_{25}H_{32}N_2O_4S \cdot HCl \cdot 0.5H_2O$: C, 59.81; H, 6.83; N, 5.58. Found: C, 59.47; H, 6.76; N, 5.29.

Example 82

N-[2-(2,3-Dihydrobenzofuran-6-yl)ethyl-N-[(R)-5,6-methylenedioxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]-N-ethylamine hydrochloride

5,6-Methylenedioxy-1,2,3,4-tetrahydronaphthalene-1-carboxylic acid was treated as decribed in Examples 10-14 and Example 107. This product (738 mg, 2.9 mmol) and 2,3-dihydrobenzo[b]furan-6-ylacetic acid (566 mg, 3.1 mmol) were treated as described in Example 19. The crude free base was chromatographed on

silica gel eluting with 3:7 ethyl acetate-hexane to give 580 mg (84%) of the title compound free base. The hydrochloride salt was prepared in ethyl acetate by the addition of hydrogen chloride in isopropyl alcohol followed by ether to give 508 mg of the title compound. m.p. 165-166 °C. The 300 MHz ^{1}H NMR spectrum was found to be consistent with the desired product. MS (DCI/NH_3) m/e 366 $(M+H)^+$. Anal calcd for $C_{24}H_{31}NO_2 \cdot HCl$: C, 71.71; H, 8.03; N, 3.49. Found: C, 71.31; H, 7.99; N, 3.37.

Example 83

N-[2-(N-Methanesulfonamido-1,3-dihydroisoindol-5-yl)ethyl-N-[(R)-5-methoxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]-N-ethylamine hydrochloride

N-Methanesulfonamido-1,3-dihydroisoindol-5-yl)acetic acid (880 mg, 3.4 mmol) and N-[(R)-5-methoxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]-N-ethylamine (800 mg, 3.1 mmol) were treated as described in Example 19 to afford 1.15 g of the free base. The free base was chromatographed twice on silica gel eluting with mixtures of ethyl acetate in hexane to give 580 mg of purified material, which was converted to a hydrochloride salt by dissolving in ethyl acetate and treating with an isopropyl alcohol solution of hydrogen chloride followed by ether to give the hydrochloride salt. m.p. 215 °C with decomposition. The 300 MHz ^{1}H NMR spectrum was found to be consistent with the desired product. MS (DCI/NH_3) m/e 443 $(M+H)^+$. Anal calcd for $C_{25}H_{34}N_2O_3 \cdot HCl$: C, 62.68; H, 7.36; N, 5.85. Found: C, 62.33; H, 7.27; N, 5.78.

Example 84

N-[2-(N-Methanesulfonamido-1,3-dihydroisoindol-5-yl)ethyl-N-[(R)-8-fluoro-5-methoxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]-N-methylamine methanesulfonate

N-[(R)-8-Fluoro-5-methoxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]-N-methylamine hydrochloride (675 mg, 2.6 mmol), resulting from Example 16, was reacted with N-methanesulfonamido-1,3-dihydroisoindol-5-yl)acetic acid (0.75 g, 2.9 mmol) by the procedure described in Example 19 to yield the title compound (980 mg, 82%). m.p. 188 °C after recrystallization from ethanol. The 300 MHz ^{1}H NMR spectrum was found to be consistent with the desired product. MS (DCI/NH_3) m/e 447 $(M+H)^+$. Anal calcd for $C_{24}H_{31}N_2O_3S \cdot CH_3SO_3H$: C, 55.33; H, 6.50; N, 5.16. Found: C, 55.45; H, 6.40; N, 5.16.

Example 85

N-[2-(N-Methanesulfonamido-1,3-dihydroisoindol-5-yl)ethyl-N-[(R)-5,6-methylenedioxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]-N-methylamine methanesulfonate

N-[(R)-5,6-Methylenedioxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]-N-methylamine hydrochloride (2.2 g, 8.6 mmol), resulting from Example 18, was reacted with N-methanesulfonamido-1,3-dihydroisoindol-5-yl)acetic acid (2.42 g, 9.5 mmol) by the procedure described in Example 2.3 g of the title compound. Recrystallization from methanol-ether gave 1.9 g (52%). m.p. 191 °C. The 300 MHz ^{1}H NMR spectrum was found to be consistent with the desired product. MS (DCI/NH_3) m/e 443 $(M+H)^+$. Anal calcd for $C_{24}H_{30}N_2O_4S \cdot CH_3SO_3H$: C, 55.74; H, 6.36; N, 5.20. Found: C, 55.47; H, 6.30; N, 5.17.

Example 86

N-[2-(2,3-Dihydrobenzofuran-6-yl)ethyl]-N-[(R)-5-ethoxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]-N-methylamine methanesulfonate

2,3-Dihydrobenzofuran-6-acetic acid (0.73 g) and the product resulting from Example 17 (1.25 g) were treated by the procedure described in Example 19 to yield 1.25 g of the desired product as a white solid. m.p. 162-163 C. ^{1}H NMR (CD_3OD, 300 MHz) δ 1.40 (t, 3H), 1.85 (m, 4H), 2.69 (s, 3H), 2.5-2.7 (m, 2H), 2.9-3.6 (m, 12H), 4.0 (q, 2H), 4.5 (t, 2H), 6.8 (m, 4H), 7.1 (m, 2H). Anal calcd for $C_{25}H_{35}NO_5S$: C, 65.05; H, 7.64; N, 3.03. Found: C, 64.76; H, 7.58; N, 3.02.

Example 87

N-[2-(2,3-Dihydrobenzofuran-7-yl)ethyl]-N-[(R)-5-methoxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]-N-methylamine methanesulfonate

2,3-Dihydrobenzofuran-7-acetic acid (0.5 g) and the product resulting from Example 15 (0.68 g) were treated by the procedure described in Example 19 to yield 0.33g of the desired product as a white solid. m.p. 122-123 °C. ^{1}H NMR (CD_3OD, 300 MHz) δ 1.85 (m, 6H), 2.5-2.8 (m, 2H), 2.7 (s, 3H), 3.0-3.5 (m, 8H), 3.8 (s, 3H), 4.6 (t, 2H), 6.8 (m, 3H), 7.0 (m, 1H), 7.15 (m, 2H). Anal calcd for $C_{25}H_{31}NO_5S$: C, 64.40; H, 7.43; N, 3.13. Found: C, 64.34; H, 7.31; N, 3.09.

Example 88

N-[2-(Benzofuran-7-yl)ethyl]-N-[(R)-5-methoxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]-N-methylamine hydrochloride

Benzofuran-7-acetic acid (0.2 g) and the product resulting from Example 15 (0.34 g) were treated by the procedure described in Example 19 to yield 0.115 g of the desired product as a white solid. m.p. 196-197 °C. ^{1}H NMR (CD_3OD, 300 MHz) δ 1.85 (m, 4H), 2.5-2.7 (m, 2H), 3.0-3.6 (m, 10H), 3.8 (s, 3H), 6.8 (m, 3H), 7.2 (m, 3H), 7.55 (m, 1H), 7.8 (m, 1H). Anal calcd for $C_{23}H_{28}ClNO_2$: C, 71.58; H, 7.31; N, 3.63. Found: C, 71.12; H, 7.15; N, 3.46.

Example 89

N-[2-(2,3-Dihydrobenzofuran-7-yl)ethyl]-N-[(R)-5,6-methylenedioxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]-N-methylamine hydrochloride

2,3 Dihydrobenzofuran-7-acetic acid (0.5 g) and the product resulting from Example 18 (0.86 g) were treated by the procedure described in Example 19 to yield 0.227 g of the desired product as a white solid. m.p. 195-196 °C. ^{1}H NMR (CD_3OD, 300 MHz) δ 1.85 (m, 4H), 2.5-2.8 (m, 2H), 3.0-3.5 (m, 12H), 4.55 (t, 2H), 5.9 (d, 2H), 6.7 (m, 2H), 6.8 (t, 1H), 7.0 (m, 1H), 7.15 (d, 1H). Anal calcd for $C_{23}H_{28}ClNO_3$: C, 68.73; H, 7.02; N, 3.48. Found: C, 68.23; H, 7.05; N, 3.32.

Example 90

N-[2-(N-Methanesulfonamido-1,3-dihydroisoindol-5-yl)ethyl]-N-[(R)-5-ethoxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]-N-methylamine methanesulfonate hemihydrate

N-Methanesulfonamido-1,3-dihydroisoindole-5-acetic acid (0.68 g) and the product resulting from Example 17 (0.63 g) were treated by the procedure described in Example 19 to yield 0.38 g of the desired product as a white solid. m.p. 163-164 °C. ^{1}H NMR (CD_3OD, 300 MHz) δ1.40 (t, 3H), 1.9 (m, 4H), 2.5-2.8 (m, 2H), 2.7 (s, 3H), 2.9 (d, 3H), 2.0-3.6 (m, 11H), 4.0 (q, 2H), 4.62 (s, 2H), 4.64 (s, 2H), 6.8 (m, 2H), 7.1 (t, 1H), 7.3 (m, 3H). Anal calcd for $C_{27}H_{39}N_2O_6S_2 \cdot H_2O$: C, 56.09; H, 6.95; N, 5.07. Found: C, 56.06; H, 6.95; N, 4.97.

Example 91

N-[2-(Quinolin-5-yl)ethyl]-N-[(R)-5-methoxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]-N-methylamine dihydrochloride

Quinoline-5-acetic acid (0.92 g, 5.5 mmol) and the product resulting from Example 15 (1.21 g, 5.0 mmol) were treated as described in Example 19. Purification and conversion to the dihydrichloride salt yielded 0.44 g of the desired product as a white solid. m.p. 120-23 °C. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 1,8 (m, 6H), 2.4-2.7 (m, 2H), 3.05 (s, 3H), 3.3-3.7 (m, 5H), 3.78 (s, 3H), 6.84 (d, 1H), 6.9 (d, 1H), 7.17 (t, 1H), 7.8 (m, 1H), 8.0 (m, 2H), 8.2 (m, 1H), 9.2 (m, 2H). Anal calcd for $C_{24}H_{30}Cl_2N_2O$: C, 66.51; H, 6.98; N, 6.47. Found: C, 66.28; H, 7.21; N, 6.40.

Example 92

N-[2-(Quinolin-8-yl)ethyl]-N-[(R)-5-methoxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]-N-methylamine dihydrochloride

Quinoline-8-acetic acid (1.84 g, 11 mmol) and the product resulting from Example 15 (2.42 g, 5.0 mmol) were treated as described in Example 19. Purification and conversion to the dihydrichloride salt yielded 0.83 g of the desired product as a white solid. m.p. 155-60 °C. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 1.7 (m, 4H), 2.1 (m, 1H), 3.2-3.9 (m, 9H), 3.78 (s, 3H), 6.8 (d, 1H), 6.96 (d, 1H), 7.15 (t, 1H), 7.7 (m, 2H), 7.85 (d, 1H), 8.0 (d, 1H), 8.6 (m, 1H), 9.0 (m, 1H). Anal calcd. for $C_{24}H_{30}Cl_2N_2O \cdot 1/2H_2O$: C, 65.15; H, 7.06; N, 6.33. Found: C, 64.88; H, 7.21; N, 6.34.

Example 93

N-[2-(Quinolin-6-yl)ethyl]-N-[(R)-5,6-methylenedioxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]-N-methylamine dihydrochloride

Quinoline-6-acetic acid (1.84 g, 11 mmol) and the product resulting from Example 18 (2.56 g, 10.0 mmol) were treated as described in Example 19. Purification and conversion to the dihydrochloride salt yielded 1.10 g of the desired product as a white solid. m.p. 260-61 °C. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 1.9 (m, 4H), 2.6 (m, 2H), 3.14 (s, 3H), 3.3-3.8 (m, 7H), 5.92 (d, 2H), 6.7 (d, 1H), 6.8 (d, 1H), 8.1-8.4 (m, 4H), 9.2 (m, 2H). Anal calcd for $C_{24}H_{28}Cl_2N_2O_2 \cdot 0.25 H_2O$: C, 63.78; H, 5.91; N, 6.20. Found: C, 63.50; H, 6.23; N, 6.07.

Example 94

N-[2-(Benzo[b]thien-3-yl)ethyl]-N-[(R)-5-methoxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]-N-methylamine methanesulfonate

Benzthiophene-3-acetic acid (1.92 g, 10 mmol) and the product resulting from Example 15 (2.42 g, 10 mmol) were treated as described in Example 19, replacing BH_3 with $LiAlH_4$ as the reducing reagent. Purification and conversion to the methanesulfonate salt yielded 1.53 g of the desired product as a white solid. m.p. 198-201 ° C. ^1H NMR (DMSO-d_6, 300 MHz) δ 1.8 (m, 4H), 2.5-2.9 (m, 2H), 2.7 (s, 3H), 3.1 (s, 3H), 3.2-3.7 (m, 7H), 3.8 (s, 3H), 6.8 (m, 2H), 7.15 (t, 1H), 7.4 (m, 3H), 7.9 (m, 2H). Anal.calcd for $C_{24}H_{31}NO_4S_2 \cdot 0.5\ H_2O$: C, 61.24; H, 6.85; N, 2.98. Found: C, 61.31; H, 6.85; N, 2.99.

Example 95

N-[2-(Benzo[b]thien-2-yl)ethyl]-N-[(R)-5-methoxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]-N-methylamine methanesulfonate

Benzthiophene-2-acetic acid (1.92 g, 10 mmol) and the product resulting from Example 15 (2.42 g, 10 mmol) were treated as described in Example 19, replacing BH_3 with $LiAlH_4$ as the reducing reagent. Purification and conversion to the methanesulfonate salt yielded 1.65 g of the desired product as a white solid. m p. 177-78 °C. ^1H NMR ($CDCl_3$, 300 MHz) δ 1.7-2.2 (m, 4H), 2.8-2.8 (m, 3H), 2.86 (s, 3H), 3.0 (s, 3H), 3.20-3.7 (m, 9H), 3.8 (s, 3H), 6.7 (m, 2H), 7.13 (t, 1H), 7.22 (s, 1H), 7.3 (m, 2H), 7.7 (m, 2H). Anal calcd for $C_{24}H_{31}NO_4S_2$: C, 62.44; H, 6.77; N, 3.03. Found: C, 62.49; H, 6.76; N, 3.10.

Example 96

N-[2-(Indol-3-yl)ethyl]-N-[(R)-5-methoxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]-N-methylamine methanesulfonate

Indole-3-acetic acid (1.75 g, 10 mmol) and the product resulting from Example 15 (2.42 g, 10 mmol) were treated as described in Example 19, replacing BH_3 with $LiAlH_4$ as the reducing reagent. Purification and conversion to the methanesulfonate salt yielded 1.32 g of the desired product as a white solid. m.p. 117-120 °C. ^1H NMR ($CDCl_3$, 300 MHz) δ 1.9 (m, 4H), 2.5-3.4 (m, 9H), 2.86 (s, 3H), 3.0 (s, 3H), 3.8 (s, 3H), 6.7 (m, 2H), 6.9-7.2 (m, 4H), 7.4 (m, 2H), 9.4 (br s, 1H). Anal calcd for $C_{24}H_{32}N_2O_4S$: C, 64.83; H, 7.26; N, 6.30. Found: C, 64.79; H, 7.26; N, 6.32.

Example 97

N-[2-(N-Trifluoromethanesulfonamido-2,3-dihydroindol-6-yl)ethyl]-N-[(R)-5-methoxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]-N-methylamine methanesulfonate

N-Trifluoromethanesulfonamido-2,3-dihydroindole-6-acetic acid (0.928 g, 3.00 mmol) and the product resulting from Example 18 (0.725 g, 3.00 mmol) were treated by the procedure described in Example 19 to yield 0.654 g of the desired product as a white solid. m.p. 140-141 °C. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 1.8 (m, 4H), 2.4-2.7 (m, 2H), 2.95 (s, 3H), 3.0-3.5 (m, 7H), 3.3 (s, 3H), 3.78 (s, 3H), 4.2 (m, 2H), 6.8 (d, 1H), 6.87 (d, 1H), 7.15 (m, 2H), 7.3 (m, 2H). Anal calcd for $C_{25}H_{33}F_3N_2O_6S_2$: C, 51.89; H, 5.75; N, 4.84. Found: C, 52.20; H, 5.73; N, 4.86.

Example 98

N-[2-(2,3-Dihydrobenzo[b]thien-5-yl)ethyl]-N-[(R)-5,6-methylenedioxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]-N-methylamine methanesulfonate

2,3-Dihydrobenzo[b]thiophene-5-acetic acid (0.510 g, 2.65 mmol) and the product resulting from Example 18 (0.639 g, 2.50 mmol) were treated by the procedures described in Example 19 to yield 0.462 g of the desired product as a white solid. m.p. 163-165 °C. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 1.7-1.9 (m, 4H), 2.3 (s, 3H), 2.5-2.7 (m, 2H), 2.95 (s, 3H), 2.9-3.5 (m, 11H), 6.0 (d, 2H), 6.8 (m, 2H), 7.0-7.3 (m, 3H). Anal calcd for $C_{24}H_{31}NO_5S_2$: C, 60.35; H, 6.54; N, 2.93. Found: C, 59.95; H, 6.51; N, 2.91.

Example 99

N-[2-(N-Methanesulfonamido-2,3-dihydroindol-6-yl)ethyl]-N-[(R)-5,6-methylenedioxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]-N-methylamine methanesulfonate

N-Methanesulfonamido-2,3-dihydroindol-6-acetic acid (0.670 g, 2.62 mmol) and the product resulting from Example 18 were treated by the procedures described in Example 19 to yield 0.605 g of the desired product as a white solid. m.p. 124-126 °C. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 1.7-1.9 (m, 4H), 2.3 (s, 3H), 2.5-2.7 (m, 4H), 2.9-3.5 (m, 10H), 3.0 (s, 3H), 3.95 (m, 2H), 6.0 (d, 2H), 6.78 (m, 2H), 7.0 (m, 1H), 7.2 (m, 2H). Anal calcd for $C_{25}H_{34}N_2O_7S_2 \cdot 0.25\ H_2O$: C, 55.28; H, 6.40; N, 5.16. Found: C, 55.08; H, 6.32; N, 5.14.

Example 100

N-[2-(2,3-Dihydroindol-5-yl)ethyl]-N-[(R)-5,6-methylenedioxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]-N-methylamine dihydrochloride

N-Benzoyl-2,3-dihydroindol-5-acetic acid (0.928 g, 3.30 mmol) and the product resulting from Example 18 (0.767 g, 3.00 mmol) were treated by the procedures described in Example 19 to yield 0.702 g of the dihydrochloride salt of the intermediate N-benzyl analog of the desired product. Hydrogenation of this intermedate in methanol in the presence of 0.07 g 10% Pd/C yielded 0.290 g of the desired product as a white solid. m.p. 246-248 °C. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 1.7-2.1 (m, 6H), 2.4-2.7 (m, 4H), 2.95 (s, 3h), 2.9-3.8 (m, 8H), 6.0 (d, 2H), 6.8 (m, 2H), 7.3 (m, 3H). Anal calcd for $C_{23}H_{30}Cl_2N_2O_2$: C, 63.16; H, 6.91; N, 6.40. Found: C, 63.30; H, 6.98; N, 6.79.

Example 101

N-[2-(Benzofuran-5-yl)ethyl]-N-[(R)-5,6-methylenedioxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]-N-methylamine methanesulfonate

Benzofuran-5-acetic acid (0.582 g, 3.30 mmol) and the product resulting from Example 18 (0.767 g, 3.00 mmol) were treated by the procedures described in Example 19, substituting $LiAlH_4$ for BH_3 as the reducing agent to yield 0.840 g of the desired product as a white solid. m.p. 171-172 °C. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 1.7-1.9 (m, 4H), 2.3 (s, 3H), 2.5-2.7 (m, 2H), 3.0 (s, 3H), 3.0-3.6 (m, 7H), 6.0 (d, 2H), 6.8 (d, 2H), 6.95 (m, 1H), 7.23 (m, 1H), 7.6 (m, 2H), 8.0 (m, 1H). Anal calcd for $C_{24}H_{29}NO_6S$: C, 62.73; H, 6.36; N, 3.05. Found: C, 62.59; H, 6.33; N, 3.02.

Example 102

N-[2-(2,2-Dioxo-1,3-dihydrobenzo[c]thien-5-yl)ethyl]-N-[(R)-5-methoxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]-N-methylamine methanesulfonate

5-(2-Bromoethyl)-2,2-dioxo-1,3-dihydrobenzo[c]thiophene (0.275 g, 1.00 mmol) and the product resulting from Example 15 (0.242 g, 1.00 mmol) were combined with ethyldiisopropyl amine (0.42 ml, 2.4 mmol) in acetonitrile (3 mL). After 5 hours at 75 °C., the product was isolated, purified and converted to its methanesulfonate salt to yield 0.237 g of the desired product as a white solid. m.p. 169-71 °C. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 1.7-2.0 (m, 4H), 2.3 (s, 3H), 2.4-2.7 (m, 4H), 3.0 (s, 3H), 3.0-3.6 (m, 7H), 3.78 (s, 3H), 4.5 (m, 4H), 6.85 (m,

2H), 7.15 (m, 1H), 7.3 (m, 3H). Anal calcd for $C_{24}H_{33}NO_6S_2$: C, 58.16; H, 6.71; N, 2.83. Found: C, 58.10; H, 6.64; N, 2.83.

Example 103

N-[2-(2,2-Dioxo-1,3-dihydrobenzo[c]thien-5-yl)ethyl]-N-[(R)-5,6-methylenedioxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]-N-methylamine methanesulfonate

5-(2-Bromoethyl)-2,2-dioxo-1,3-dihydrobenzo[c]thiophene (0.350 g, 1.27 mmol) and the product resulting from Example 18 (0.325 g, 1.27 mmol) were combined with ethyldiisopropyl amine (0.54 ml, 2.6 mmol) in acetonitrile (3 mL). After 5 hours at 75 °C., the product was isolated, purified and converted to its methanesulfonate salt to yield 342 mg of the desired product as a white solid. m.p. 177-179 °C. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 1.7-1.9 (m, 4H), 2.35 (s, 3H), 2.5-2.7 (m, 2H), 2.95 (s, 3H), 3.0-3.7 (m, 7H), 4.5 (m, 4H), 6.0 (d, 2H), 6.8 (m, 2H), 7.3-7.4 (m, 3H). Anal calcd for $C_{24}H_{31}NO_7S_2$: C, 56.56; H, 6.13; N, 2.75. Found: C, 56.51; H, 6.13; N, 2.69.

Example 104

N-[2-(Benzofuran-7-yl)ethyl]-N-[(R)-5,6-methylenedioxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]-N-methylamine methanesulfonate

Benzofuran-7-acetic acid (0.352 g, 2.00 mmol) and the product resulting from Example 18 (0.511 g, 2.00 mmol) were treated by the procedures described in Example 19, substituting $LiAlH_4$ for BH_3 as the reducing agent to yield 0.447 g of the desired product as a white solid. m.p. 142-143 °C. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 1.7-1.9 (m, 4H), 2.3 (s, 3H), 2.5-2.7 (m, 2H), 3.0 (s, 3H), 3.0-3.6 (m, 7H), 6.0 (d, 2H), 6.8 (d, 2H), 7.0 (m, 1H), 7.2-7.3 (m, 2H), 7.6 (m, 1H), 8.1 (m, 1H). Anal calcd for $C_{24}H_{29}NO_6S$: C, 62.73; H, 6.36; N, 3.05. Found: C, 62.59; H, 6.15; N, 2.98.

Example 105

N-[2-(3-Methyl-benzofuran-5-yl)ethyl]-N-[(R)-5-methoxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]-N-methylamine methanesulfonate

3-Methylbenzofuran-5-acetic acid (0.94 g) and the product resulting from Example 15 (1.0 g) were treated by the procedure described in Example 19, substituting lithium aluminum hydride for borane, to yield 1.12 g of the desired product as a white solid. m.p. 164.5-165.5°C. ^{1}H NMR ($CDCl_3$, 300 MHz) of the free base δ 1.55-2.0 (m, 4H), 2.2 (s, 3H), 2.4-3.0 (m, 12H), 3.81 (s, 3H),

6.70 (d, 1H), 6.82 (d, 1H), 7.1 (m, 2H), 7.35 (m, 3H). Anal calcd for $C_{25}H_{33}NO_5S$: C, 65.33; H, 7.24; N, 3.05. Found: C, 65.21; H, 7.08; N, 3.03.

Example 106

N-[2-(2-Methyl-benzofuran-5-yl)ethyl]-N-[(R)-5-methoxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]-N-methylamine methanesulfonate

2-Methylbenzofuran-5-acetic acid (1.00 g) and the product resulting from Example 15 (1.40 g) were treated by the procedure described in Example 19, substituting lithium aluminum hydride for borane to yield 1.23 g of the desired product as a white solid. m.p. 161-162°C. ^{1}H NMR ($CDCl_3$, 300 MHz) of the free base δ 1.5-2.0 (m, 4H), 2.45 (s, 3H), 2.35-3.0 (m, 12H), 3.81 (s, 3H), 6.3 (bs, 1H), 6.55 (d, 1H), 6.8 (d, 1H), 7.05 (t, 2H). Anal calcd for $C_{25}H_{33}NO_5S$: C, 65.33; H, 7.24; N, 3.05. Found: C, 65.39; H, 7.35; N, 3.00.

Example 107

N-[2-(2,3-Dihydrobenzo[b]thien-5-yl)ethyl]-N-[(R)-5-methoxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]-N-ethylamine hydrochloride

The product resulting from Example 14 (2.27 g, 10.0 mmol) was treated with acetic anhydride (1.5 g, 15 mmol) in pyridine (10 mL) to yield the intermediate N-acetyl derivative, which was reduced with BH_3·THF by the procedures described in Example 15 to yield 2.05 g of the N-ethyl derivative. 2,3-Dihydrobenzothiophene-5-acetic acid (0.63 g) and the N-ethyl amine hydrochloride product (0.69 g) were treated by the procedure described in Example 19 but converting instead to the hydrochloride salt to yield 0.52 g of the desired product as a white solid. m.p. 181-182 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) of the free base δ 1.42 (t, 3H), 1.75 (m, 3H), 1.95 (m, 1H), 2.35 (bs, 3H), 2.3-2.9 (m, 4H), 3.2-3.4 (m, 4H), 3.81 (s, 3H), 4.2 (m, 2H), 6.55 (d, 1H), 6.8 (d, 1H), 6.95 (d, 1H), 7.05 (s, 1H), 7.1 (t, 2H). Anal calcd for $C_{24}H_{32}ClNOS$: C, 68.96; H, 7.72; N, 3.35. Found: C, 68.67; H, 7.65; N, 3.28.

Example 108

N-[2-(Benzofuran-6-yl)ethyl]-N-[(R)-5-methoxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]-amine hydrochloride

Benzofuran-6-acetic acid (0.085 g) and the product resulting from Example 14 (0.10 g) were treated by the procedure described in Example 19, substituting lithium aluminum hydride for borane and converting instead to the hydrochloride

salt to yield 0.12 g of the desired product as a white solid. m.p. 193-194 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) of the free base δ 1.5-1.8 (m, 4H), 2.5-3.0 (m, 10H), 2.95 (s, 3H), 3.81 (s, 3H), 6.65 (d, 1H), 6.75 (m, 2H), 7.05 (m, 2H), 7.47 (s, 1H), 7.5 (d, 1H), 7.6 (d, 1H). Anal calcd for $C_{22}H_{26}ClNO_2 \cdot 0.25\ H_2O$: C, 70.20; H, 7.10; N, 3.72. Found: C, 70.34; H, 7.00; N, 3.73.

Example 109

N-[3-(2-(1,2-Benzisothiazolin-3-one-1,1-dioxide))propyl]-N-[(R)-5-methoxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]-N-methylamine hydrochloride

The product resulting from Example 15 (0.65 g) was dissolved in 25 mL of acetonitrile and 1.4 mL diisopropylethylamine. To the reaction was added 0.90 g 3-bromopropyl-2-1,2-benzisothiazolin-3-one-1,1-dioxide, and the reaction was heated at reflux for 4 hours. The reaction was quenched in 5% $NaHCO_3$, extracted with ether, dried (K_2CO_3), and evaporated to dryness. The product, after chromatography, was treated with ethereal HCl, and then recrystallized from ethyl acetate to yield 0.57 g of the desired product as a white solid. m.p. 186-188 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) of the free base δ 1.75 (m, 3H), 2.0 (m, 3H), 2.3 (s, 3H), 2.25-2.6 (m, 4H), 2.75 (m, 1H), 2.95 (m, 1H), 3.81 (s, 3H), 3.85 (m, 3H), 6.65 (d, 1H), 6.82 (d, 1H), 7.1 (t, 1H), 7.85 (m, 3H), 8.05 (dd, 1H). Anal calcd for $C_{23}H_{29}ClN_2O_4S$: C, 59.41; H, 6.29; N, 6.02. Found: C, 59.06; H, 6.19; N, 5.89.

Example 110

N-[3-(2-(1,2-benzisothiazolin-3-one-1,1-dioxide))ethyl]-N-[(R)-5-methoxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]-N-methylamine hydrochloride

The product resulting from Example 15 (0.50 g) was dissolved in 25 mL acetonitrile and 1.25 mL diisopropylethylamine. To the reaction mixture was added 0.72 g 2-bromoethyl-2-(1,2-benzisothiazolin-3-one-1,1-dioxide), and the reaction was heated at reflux for 4 hours. The reaction was quenched in 5% $NaHCO_3$, extracted with ether, dried (K_2CO_3), and evaporated to dryness. The product, after chromatography, was treated with ethereal HCl, and then recrystallized from ethyl acetate to yield 0.23 g of the desired product as a white solid. m.p. 135-147 °C. ^{1}H NMR (DMSO-d_6, 300 MHz) of the hydrochloride salt δ 1.65-2.0 (m, 4H), 2.4-2.7 (m, 3H), 3.0 (d, 3H), 3.3-3.6 (m, 4H), 3.8 (s, 3H), 4.25 (m, 2H), 6.8 (d, 1H), 6.9 (d, 1H), 7.15 (m, 1H), 8.1 (m, 3H), 8.35 (m, 1H). Anal calcd for $C_{22}H_{27}ClN_2O_4S$: C, 58.59; H, 6.03; N, 6.21; S, 7.11. Found: C, 58.54; H, 6.14; N, 6.08; S, 6.99.

Example 111

N-[2-(2,3-Dihydrobenzofuran-6-yl)ethyl]-N-[(R)-5,6-methylenedioxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]-N-methylamine methanesulfonate

2,3-Dihydrobenzofuran-6-acetic acid (0.50 g) and the product resulting from Example 18 (0.60 g) were treated by the procedure described in Example 19 to yield 0.63 g of the desired product as a white solid. m.p. 179-180 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) of the free base δ 1.7-2.25 (m, 4H), 2.83 (s, 3H), 2.5-3.5 (m, 11H), 4.55 (q, 2H), 5.95 (m, 2H), 6.55-6.7 (m, 4H), 7.15 (t, 1H). Anal calcd for $C_{24}H_{31}NO_6S$: C, 62.45; H, 6.77; N, 3.03. Found: C, 62.19; H, 6.75; N, 3.09.

Example 112

N-[2-(2,3-Dihydrobenzo[b]thien-5-yl)ethyl]-N-[(R)-5-ethoxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]-N-methylamine methanesulfonate

2,3-Dihydrobenzothiophene-5-acetic acid (0.69 g) and the product resulting from Example 17 (0.75 g) were treated by the procedure described in Example 19 to yield 0.96 g of the desired product a a white solid. m.p. 152-153 °C. ^{1}H NMR (DMSO-d_6, 300 MHz) of the free base δ 1.42 (t, 4H), 1.75 (m, 6H), 2.3 (s, 3H), 2.6-3.5 (m, 5H), 2.9 (d, 2H), 3.0 (d, 2H), 4.0 (m, 3H), 6.8 (d, 1H), 6.85 (d, 1H), 7.0 (d, 1H), 7.15 (m, 3H). Anal calc for $C_{25}H_{35}NO_4S_2$: C, 62.86; H, 7.39; N, 2.93. Found: C, 62.82; H, 7.32; N, 2.89.

Example 113

5-{2-[((R)-5,6-Methylenedioxy-1,2,3,4-tetrahydro-naphthalen-1-ylmethyl)methyl-aminol-ethyl}-1,3-dihydro-indol-2-one hydrochloride

5-(2-bromoethyl)-2,3-dihydroindol-2-one (1.68 g), the product resulting from Example 18 (0.78 g), and diisopropyl ethyl amine (0.73 ml) were combined in acetonitrile and heated at 60°C for 18 hours. The reaction was quenched in 5% $NaHCO_3$ and extracted with ethyl acetate. The combined organic extracts were washed with water and brine, dried over sodium sulfate, and evaporated to dryness. After chromatographic purification and conversion to the hydrochloride salt, the desired product (0.86 g) was obtained as a white solid. m.p. 286°C (dec) ^{1}H NMR ($CDCl_3$, 300 MHz) of the free base δ 1.7 (m, 3H), 1.9 (m, 1H), 2.35 (s, 3H), 2.3-2.95 (m, 9H), 3.5 (s, 2H), 5.9 (dd, 2H), 6.65 (q, 2H), 6.7 (d, 1H), 7.05 (d, 1H), 7.1 (s, 1H), 8.75 (s, 1H). Anal calcd for $C_{23}H_{27}ClN_2O_3$: C, 66.58; H, 6.56; N, 6.75. Found: C, 66.52; H, 6.53; N, 6.56.

Example 114

N-[2-(2-Chloro-benzothiazol-6-yl)-ethyl]-N-{(R)-5,6-methylenedioxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]-N-methylamine methanesulfonate

2-Chlorobenzothiazole-6-acetic acid (1.74 g) and the product resulting from Example 18 (1.63 g) were treated by the procedure described in Example 37 to yield 0.63 g of the desired product as a white solid. m.p. 143.5-145 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) of the free base δ 1.5-1.75 (m, 4H), 1.88 (m, 1H), 2.35 (s, 3H), 2.3-2.95 (m, 8H), 5.9 (dd, 2H), 6.65 (q, 2H), 7.35 (dd, 1H), 7.6 (s, 1H), 7.85 (d, 1H). Anal calcd for $C_{23}H_{27}ClN_2O_5S_2$: C, 54.06; H, 5.33; N, 5.48. Found: C, 54.08; H, 5.18; N, 5.55.

Example 115

N-[2-(Benzothiazol-6-yl)-ethyl]-N-{(R)-5,6-methylenedioxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]-N-methylamine methanesulfonate

Benzothiazole-6-acetic acid (1.74 g) and the product resulting from Example 18 (1.63 g) were treated by the procedure described in Example 51, converting instead to the methanesulfonate salt, to yield 0.40 g of the desired product as a white solid. m.p. 180-181 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) of the free base δ 1.55-1.8 (m, 4H), 1.9 (m, 1H), 2.4 (s, 3H), 2.3-3.0 (m, 8H), 5.9 (dd, 2H), 6.3 (q, 1H), 7.37 (dd, 1H), 7.8 (s, 1H), 8.05 (d, 1H), 8.95 (s, 1H). Anal calcd for $C_{23}H_{28}N_2O_5S_2$: C, 57.96; H, 5.92; N, 5.88. Found: C, 57.72; H, 5.89; N, 5.84.

Example 116

N-[2-(N-Methanesulfonamido-1,3-dihydroisoindol-5-yl)ethyl]-N-[(R)-5,6-methylenedioxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]-N-methylamine hydrochloride

N-Methanesulfonamido-1,3-dihydroisoindole-5-acetic acid (0.58 g) and the product resulting from Example 18 (0.46 g) were treated by the procedure described in Example 19, converting instead to the hydrochloride salt, to yield 0.76 g of the desired product as a white solid. m.p. 244 °C (dec). ^{1}H NMR ($CDCl_3$, 300 MHz) of the free base δ 1.5 (m, 4H), 1.7 (m, 4H), 2.65 (m, 2H), 2.55-2.8 (m, 8H), 2.85 (s, 3H), 4.58 (s, 4H), 5.92 (s, 2H), 6.6 (s, 2H), 7.1 (bs, 1H), 7.15 (m, 2H). Anal calcd for $C_{23}H_{29}ClN_2O_4S$: C, 59.41; H, 6.29; N, 6.02. Found: C, 59.48; H, 6.33; N, 6.03.

Example 117

6-{2-[((R)-5-,6-Methylenedioxy-1,2,3,4-tetrahydro-naphthalen-1-ylmethyl)methyl-amino]-ethyl}-3H-benzoxazol-2-one hydrochloride

4-Nitro-3-hydroxyphenylacetic acid (2.16 g) and the product resulting from Example 18 (2.0 g) were treated by the procedure described in Example 69 to yield 0.82 g of the desired product as a white solid. m.p. 255-256.5 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) of the free base δ 1.7 (m, 4H), 1.88 (m, 1H), 2.35 (s, 3H), 2.3-2.9 (m, 9H), 5.93 (dd, 2H), 6.65 (q, 2H), 6.97 (m, 2H), 7.10 (s, 1H). Anal calcd for $C_{22}H_{25}ClN_2O_4$: C, 63.38; H, 6.04; N, 6.72. Found: C, 63.55; H, 6.09; N, 6.68.

Example 118

N-[2-(2-Amino-benzothiazol-6-yl)-ethyl]-N-{(R)-5,6-methylenedioxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl}-N-methylamine dihydrochloride

2-Amino-benzothiazole-6-acetic acid (1.47 g) and the product resulting from Example 18 (1.5 g) were treated by the procedure described in Example 61, converting instead to the bis-hydrochloride salt, to yield 0.60 g of the desired product as a white solid. m.p. 174-176 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) of the free base δ 1.7 (m, 4H), 1.9 (m, 1H), 2.35 (s, 3H), 2.3-2.9 (m, 8H), 5.15 (bs, 2H). 5.92 (dd, 2H), 6.65 (q, 2H), 7.15 (dd, 1H), 7.45 (m, 2H). Anal calcd for $C_{22}H_{27}Cl_2N_3O_2S$: C, 56.65; H, 5.40; N, 9.01. Found: C, 57.15; H, 5.99; N, 9.05.

Example 119

N-[2-(Benzoxazol-6-yl)-ethyl]-N-{(R)-5,6-methylenedioxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl}-N-methylamine hydrochloride

4-Nitro-3-hydroxyphenylacetic acid (2.16 g) and the product resulting from Example 18 (2.0 g) were treated by the procedure described in Example 28, converting instead to the hydrochloride salt, to yield 0.38 g of the desired product as a white solid. m.p. 212-213 °C. ^{1}H NMR (DMSO-d_6, 300 MHz) of the hydrochloride salt δ 1.8 (m, 4H), 2.0 (m, 1H), 2.5 (s, 3H), 2.4-2.7 (m, 3H), 2.8-3.8 (m, 7H), 6.0 (d, 2H), 6.8 (m, 2H), 7.4 (m, 1H), 7.8 (s, 2H), 8.75 (s, 1H). Anal calcd for $C_{22}H_{25}ClN_2O_3 \cdot 0.25\ H_20$: C, 65.18; H, 6.34; N, 6.91. Found: C, 65.11; H, 6.44; N, 6.65.

Example 120

N-[2-(Benzo[b]thien-5-yl)ethyl]-N-[(R)-5,6-Methylenedioxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]-N-methylamine hydrochloride

Benzothiophene-5-acetic acid (1.0 g) and the product resulting from Example 18 (1.32 g) were treated by the procedure described in Example 19, converting instead to the hydrochloride salt, to yield 0.97 g of the desired product as a white solid. m.p. 235-236 °C. ^{1}H NMR (DMSO-d_6, 300 MHz) of the hydrochloride salt δ 1.8 (m, 3H), 2.05 (m, 1H), 2.5-2.7 (m, 4H), 2.9 (d, 3H), 3.1-3.6 (m, 5H), 6.0 (d, 2H), 6.8 (m, 2H), 7.3 (dd, 1H), 7.65 (t, 1H), 7.8 (m, 2H), 7.85 (s, 1H), 8.0 (t, 1H). Anal calcd for $C_{23}H_{26}ClNO_2S$: C, 66.41; H, 6.30; N, 3.37. Found: C, 66.34; H, 6.41; N, 3.28.

Example 121

N-[2-(Benzofuran-6-yl)ethyl]-N-[(R)-5,6-methylenedioxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]-N-methylamine methanesulfonate

Benzofuran-6-acetic acid (0.76 g) and the product resulting from Example 18 (1.00 g) were treated by the procedure described in Example 19 to yield 0.84 g of the desired product as a white solid. m.p. 128-129.5 °C ^{1}H NMR ($CDCl_3$, 300 MHz) of the free base δ 1.6 (bs, 1H), 1.7 (bs, 3H), 1.9 (bs, 1H), 2.4 (s, 3H), 2.5-3.0 (m, 9H), 5.9 (dd, 2H), 6.65 (q, 2H), 6.75 (s, 1H), 7.1 (dd, 1H), 7.35 (bs, 1H), 7.5 (d, 1H), 7.6 (d, 1H). Anal calcd for $C_{24}H_{29}NO_6S$: C, 62.73; H, 6.36; N, 3.05. Found: C, 62.89; H, 6.38; N, 3.04.

Example 122

N-[2-(2,3-Dihydrobenzofuran-4-yl)ethyl]-N-[(R)-5-methoxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]-N-methylamine methanesulfonate

2,3-Dihydrobenzofuran-4-acetic acid (0.65 g) and the product resulting from Example 15 (0.88 g) were treated by the procedure described in Example 19 to yield 1.10 g of the desired product as a white solid. m.p. 189-190.5 °C ^{1}H NMR ($CDCl_3$, 300 MHz) of the free base δ 1.7 (m, 4H), 2.3 (s, 3H), 2.5 (m, 4H), 3.0, (m, 4H), 3.3 (m, 3H), 3.4 (s, 3H), 3.78 (s, 3H), 4.5 (m, 2H), 6.7 (m, 2H), 6.85 (m, 2H), 7.1 (m, 2H). Anal calcd for $C_{24}H_{33}NO_5S$: C, 64.40; H, 7.43; N, 3.13. Found: C, 64.29; H, 7.18; N, 3.05.

Example 123

N-[2-(2,3-Dihydrobenzofuran-4-yl)ethyl]-N-[(R)-5,6-methylenedioxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]-N-methylamine methanesulfonate

2,3-Dihydrobenzofuran-4-acetic acid (0.65 g) and the product resulting from Example 18 (0.93 g) were treated by the procedure described in Example 19 to yield 0.89 g of the desired product as a white solid. m.p. 175.5-176.5 °C ^{1}H NMR (DMSO-d_6, 300 MHz) of the free base δ 1.8 (m, 4H), 2.33 (s, 3H), 2.5-2.7 (m, 3H), 2.95 (s, 3H), 3.1-3.4 (m, 7H), 4.5 (m, 2H), 6.0 (d, 2H), 6.6-6.8 (m, 4H), 7.05 (t, 1H). Anal calcd for $C_{24}H_{31}NO_6S$: C, 62.45; H, 6.77; N, 3.03. Found: C, 62.23; H, 6.67; N, 3.01.

Example 124

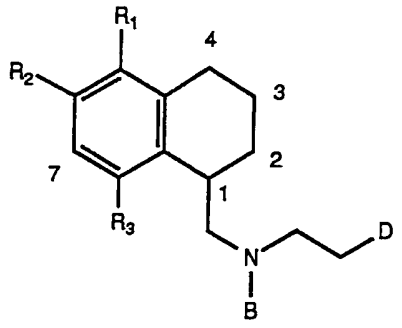
N-[2-(1,1-Dioxo-2,3-dihydrobenzo[b]thien-5-yl)ethyl]-N-[(R)-5-methoxy 1,2,3,4-tetrahydronaphthalen-1-ylmethyl]-N-methylamine hydrochloride

5-(2-Bromoethyl)-1,1-dioxo-2,3-dihydrobenzo[b]thiophene (0.315 g, 1.15 mmol) and the product resulting from Example 15 (0.332 g, 1.38 mmol) were combined with diisopropylethylamine (0.50 mL, 2.8 mmol) in acetonitrile (3 mL). After 6 hours at 75C, the product was isolated and converted to its hydrochloride salt to yield 0.147 g of the desired product as a white solid. m.p. 226-226C. ^{1}H NMR (CD_3OD, 300 MHz) δ 1.8-2.0 (m, 4H), 2.5-2.9 (m, 2H), 3.0-3.6 (m, 14H), 3.81 (s, 3H), 6.8 (m, 2H), 7.15 (t, 1H), 7.4-7.5 (m, 2H), 7.7 (m, 1H). Calc. for $C_{23}H_{30}ClNO_3S$: C, 63.36; H, 6.94; N, 3.21. Found: C, 63.18; H, 6.90; N, 3.10.

The foregoing is merely illustrative of the invention and is not intended to limit the invention to the disclosed compounds. Variations and changes which are obvious to one skilled in the art are intended to be within the scope and nature of the invention which are defined in the appended claims.

WE CLAIM:

1. A compound of the formula:



or a pharmaceutically acceptable salt thereof, wherein

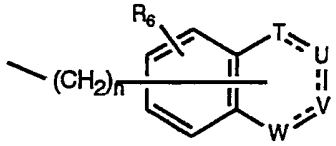
R_1 is alkoxy of from one to four carbon atoms;

R_2 is hydrogen or taken together with R_1 is methylenedioxy or ethylenedioxy;

R_3 is hydrogen, fluorine, or chlorine;

B is hydrogen or alkyl of from one to three carbon atoms; and

D is selected from the group consisting of

(a) 

wherein

n is 0, 1, or 2, and

T, U, V, and W are independently selected from

$>CH_2$,

=CH-,

>C=O,

>O, $>N-R_8$,

=N-,

>S,

>S(O), and

$>SO_2$, and

the dotted lines represent optional double bonds and

R_8 is selected from the group consisting of hydrogen, alkyl of from one to four atoms, and alkylsulfonyl;

with the provisos that

(i) when there is a double bond between T and U or V and W, then the bond between U and V is a single bond,

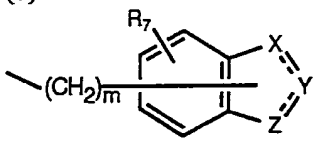
(ii) no more than three of T, U, V, and W are nitrogen,

(iii) no more than two of T, U, V, and W are oxygen, and then not in contiguous positions, and T and W may not simultaneously be oxygen,

(iv) no more than two of T, U, V, and W are sulfur, and

(v) no more than two of T, U, V, and W are >C=O; and

(b)



wherein

m is 0, 1, or 2, and

X, Y, and Z are independently selected from

$>CH_2$,

=CH-,

>C=O,

>O,

$>N\text{-}R_8$,

=N-,

>S,

>S(O), and

$>SO_2$, and

the dotted lines represent optional double bonds, and

R_8 is selected from the group consisting of hydrogen, alkyl of from one to four atoms, and alkylsulfonyl;

with the provisos that

(i) there may be only one double bond between either X and Y or between Y and Z,

(ii) no more than one of X, Y, and Z is oxygen,

(iii) no more than two of X, Y, and Z are sulfur,

(v) no more than two of X, Y, and Z are >C=O; and

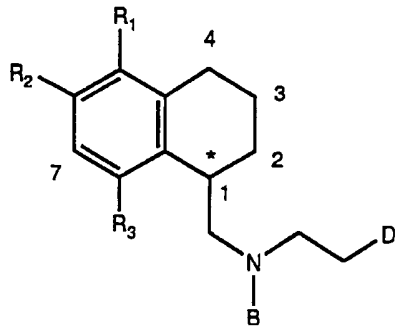
R_6 is one, two, or three substituents independently selected from the group consisting of

hydrogen,
alkyl of from one to four carbon atoms,
halogen,
hydroxy,
alkoxy of from one to four carbon atoms,
amino, and
thioalkoxy of from one to four carbon atoms; and

R_7 is one, two, or three substituents independently selected from the group consisting of

hydrogen,
alkyl of from one to four carbon atoms,
halogen,
hydroxy,
alkoxy of from one to four carbon atoms,
amino, and
thioalkoxy of from one to four carbon atoms.

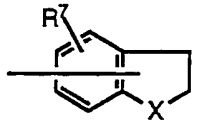
2. A compound or pharmaceutically acceptable salt thereof as defined by Claim 1 wherein the stereochemistry at the asymmetric center (*),



position-1 on the tetrahydronaphthalene, of is the R configuration and B, D, R_1, R_2, and R_3 are as defined therein.

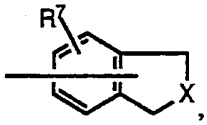
3. A compound or pharmaceutically acceptable salt thereof as defined by Claim 1wherein D is selected from the group consisting of

(a)



, and

(b)

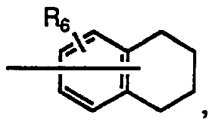


,

wherein X is selected from $>CH_2$, >O, >S, >SO, $>SO_2$, and >N-R_8 where R_8 is selected from hydrogen, lower alkyl, and alkylsulfonyl.

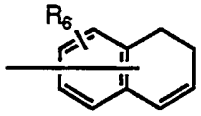
4. A compound or pharmaceutically acceptable salt thereof as defined by Claim 1 wherein D is selected from the group consisting of

(a)



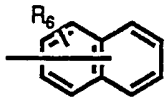
,

(b)



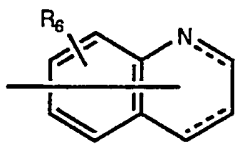
, and

(c)

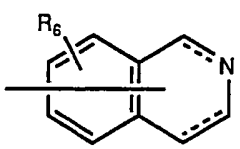


.

5. A compound or pharmaceutically acceptable salt thereof as defined by Claim 1 wherein D is selected from the group consisting of

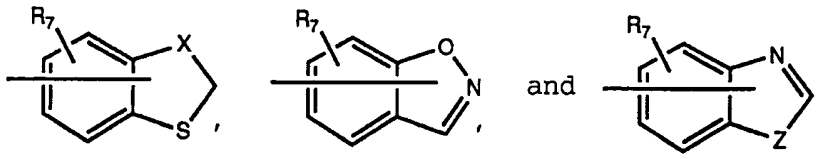


and



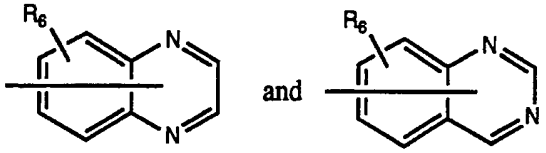
wherein R_6 is as defined therein.

6. A compound or pharmaceutically acceptable salt thereof as defined by Claim 1 wherein D is selected from the group consisting of



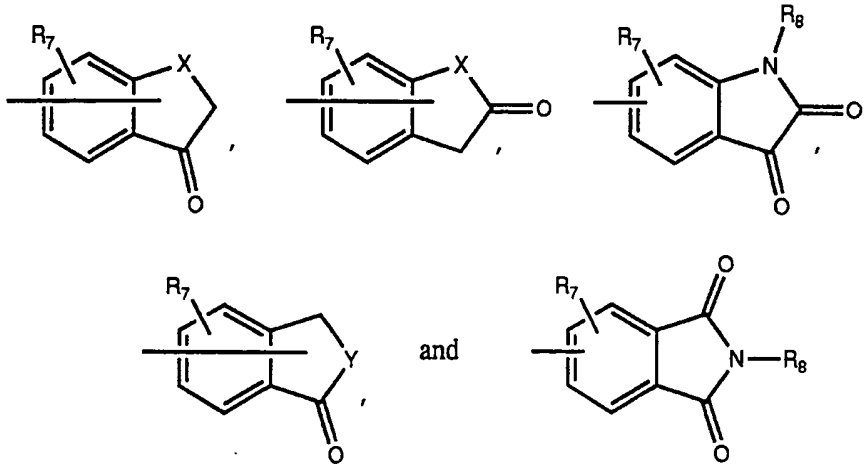
wherein X is selected from >O and >S and Z is selected from the group consisting of >O, >S, >SO, and $>SO_2$.

7. A compound or pharmaceutically acceptable salt thereof as defined by Claim 1 wherein D is selected from the group consisting of



where R_6 is as defined therein.

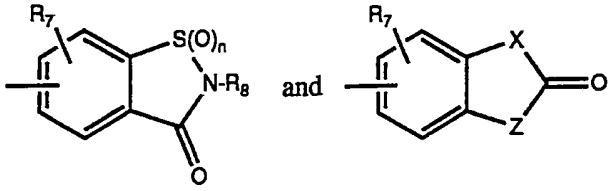
8. A compound or pharmaceutically acceptable salt thereof as defined by Claim 1 wherein D is selected from the group consisting of



R_6 and R_7 are as defined thereion and X and Y are independently selected

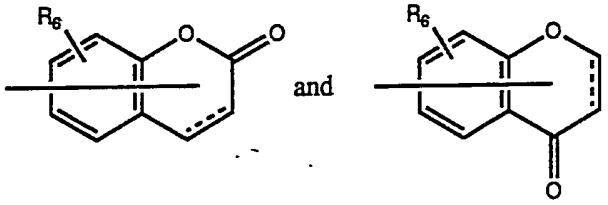
from the group consisting of >O, >S, >SO, >SO_2, and >N-R_8 where R_8 is selected from hydrogen, lower alkyl, and alkylsulfonyl.

9. A compound or pharmaceutically acceptable salt thereof as defined by Claim 1 wherein D is selected from



wherein n is 0, 1, or 2 and X and Z are independently selected from >O, >S, >SO, >SO_2, and >N-R_8 where R_8 is selected from hydrogen, lower alkyl, and alkylsulfonyl.

10. A compound or pharmaceutically acceptable salt thereof as defined by Claim 1 wherein D is selected from



where R_6 is as defined therein and the dotted line indicates an optional double bond.

11. A compound as defined by Claim 1 selected from the group consisting of:

N-[2-(2,3-Dihydrobenzofuran-5-yl)ethyl]-N-[(R)-5-methoxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]-N-methylamine;

N-[2-(Benzofuran-5-yl)ethyl]-N-[5-methoxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]-N-methylamine;

N-[2-(2,3-Dihydrobenzofuran-5-yl)ethyl]-N-[(R)-5-methoxy-8-fluoro-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]-N-methylamine;

N-[2-(Benzofuran-6-yl)ethyl]-N-[(R)-5-methoxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]-N-methylamine;

N-[2-(2,3-Dihydrobenzofuran-5-yl)ethyl]-N-[(R)-5-ethoxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]-N-methylamine;

N-[2-(2,3-Dihydrobenzofuran-6-yl)ethyl]-N-[(R)-5-methoxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]-N-methylamine;

N-[2-(2,3-Dihydrobenzofuran-5-yl)ethyl]-N-[(R)-5,6-methylenedioxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]-N-methylamine;

N-[2-(2,3-Dihydrobenzo[b]thien-5-yl)ethyl]-N-[(R)-5-methoxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]-N-methylamine;

N-[2-(Benzimidazol-5-yl)ethyl]-N-[(R)-5-methoxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]-N-methylamine;

N-[2-(Benzoxazol-6-yl)ethyl]-N-[(R)-5-methoxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]-N-methylamine;

N-[2-(Benzoxazol-5-yl)ethyl]-N-[(R)-5-methoxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]-N-methylamine;

N-[2-(Benzoxazol-6-yl)ethyl]-N-[(R)-8-fluoro-5-methoxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]-N-methylamine;

N-[2-(Benzoxazol-5-yl)ethyl]-N-[(R)-8-fluoro-5-methoxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]-N-methylamine;

N-[2-([4H]-2,3-Dihydrobenzopyran-6-yl)ethyl]-N-[(R)-5-methoxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]-N-methylamine;

N-[2-(Indan-5-yl)ethyl]-N-[(R)-5-methoxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]-N-methylamine;

N-[2-(N-Methanesulfonamido-2,3-dihydroindol-5-yl)ethyl]-N-[(R)-5-methoxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]-N-methylamine;

N-[2-(Benzimidazol-5-yl)ethyl]-N-[(R)-8-fluoro-5-methoxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]-N-methylamine;

N-[2,3-Dihydroindol-5-yl)ethyl]-N-[(R)-5-methoxy-1,2,3,4-tetrahydro-naphthalen-1-ylmethyl]-N-methylamine,

N-[2-(2-Chlorobenzothiazol-6-yl)ethyl]-N-[(R)-5-methoxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]-N-methylamine;

N-[2-(Quinoxalin-6-yl)ethyl]-N-[(R)-5-methoxy-1,2,3,4-tetrahydro-naphthalen-1-ylmethyl]-N-methylamine;

N-[2-(Quinolin-6-yl)ethyl]-N-[(R)-5-methoxy-1,2,3,4-tetrahydro-naphthalen-1-ylmethyl]-N-methylamine;

N-[2-(Quinolin-7-yl)ethyl]-N-[(R)-5-methoxy-1,2,3,4-tetrahydro-naphthalen-1-ylmethyl]-N-methylamine;

N-[2-(Isoquinolin-6-yl)ethyl]-N-[(R)-5-methoxy-1,2,3,4-tetrahydro-naphthalen-1-ylmethyl]-N-methylamine;

N-[2-(Isoquinolin-7-yl)ethyl]-N-[(R)-5-methoxy-1,2,3,4-tetrahydro-naphthalen-1-ylmethyl]-N-methylamine;

N-[2-(N-Methanesulfonamido-2,3-dihydroindol-6-yl)ethyl]-N-[(R)-5-methoxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]-N-methylamine;

N-[2-(N-Propanesulfonamido-2,3-dihydroindol-6-yl)ethyl]-N-[(R)-5-methoxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]-N-methylamine;

N-[2-(N-Isobutanesulfonamido-2,3-dihydroindol-6-yl)ethyl]-N-[(R)-5-methoxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]-N-methylamine;

N-[2-(N-Methyl-2,3-dihydroindol-5-yl)ethyl]-N-[(R)-5-methoxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]-N-methylamine;

N-[2-(N-Methyl-2,3-dihydroindol-6-yl)ethyl]-N-[(R)-5-methoxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]-N-methylamine;

N-[2-(2,3-Dihydroindol-6-yl)ethyl]-N-[(R)-5-methoxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]-N-methylamine;

N-[2-(2,3-Dihydroindol-5-yl)ethyl]-N-[(R)-5-methoxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]-N-methylamine;

N-[2-(Indol-6-yl)ethyl]-N-[(R)-5-methoxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]-N-methylamine;

N-[2-(N-Methanesulfonamido-1,3-dihydroisoindol-5-yl)ethyl]-N-[(R)-5-methoxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]-N-methylamine;

N-[2-(N-Methyl-1,3-dihydroisoindol-5-yl)ethyl]-N-[(R)-5-methoxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]-N-methylamine;

N-[2-(1,3-Dihydroisoindol-5-yl)ethyl]-N-[(R)-5-methoxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]-N-methylamine;

N-[2-(Benzothiazol-6-yl)ethyl]-N-[(R)-5-methoxy-1,2,3,4-tetrahydro-naphthalen-1-ylmethyl]-N-methylamine;

N-[2-(2-Chlorobenzothiazol-5-yl)ethyl]-N-[(R)-5-methoxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]-N-methylamine;

N-[2-(Benzothiazol-5-yl)ethyl]-N-[(R)-5-methoxy-1,2,3,4-tetrahydro-naphthalen-1-ylmethyl]-N-methylamine;

N-[2-(Benzo[b]thien-5-yl)ethyl]-N-[(R)-5-methoxy-1,2,3,4-tetrahydro-naphthalen-1-ylmethyl]-N-methylamine;

N-[2-(2,3-Dihydro-benzo[b]thien-6-yl)ethyl]-N-[(R)-5-methoxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]-N-methylamine;

N-[2-(Benzo[b]thien-6-yl)ethyl]-N-[(R)-5-methoxy-1,2,3,4-tetrahydro-naphthalen-1-ylmethyl]-N-methylamine;

N-[2-(1-Oxo-2,3-dihydrobenzo[b]thien-5-yl)ethyl]-N-[(R)-5-methoxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]-N-methylamine;

N-[2-(1,1-Dioxo-2,3-dihydrobenzo[b]thien-5-yl)ethyl]-N-[(R)-5-methoxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]-N-methylamine;

N-[2-(1-Oxo-2,3-dihydrobenzo[b]thien-6-yl)ethyl]-N-[(R)-5-methoxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]-N-methylamine;

N-[2-(1,1-Dioxo-2,3-dihydrobenzo[b]thien-6-yl)ethyl]-N-[(R)-5-methoxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]-N-methylamine;

N-[2-(1,3-Dihydro-isobenzofuran-5-yl)-ethyl]-N-{(R)-5-methoxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]-N-methylamine;

N-[2-(Benzo[1,3]oxathiol-5-yl)-ethyl]-N-{(R)-5-methoxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]-N-methylamine;

N-[2-(2-Amino-benzothiazol-5-yl)-ethyl]-N-{(R)-5-methoxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]-N-methylamine;

N-[(2-Benzofuran-5-yl)-ethyl]-N-{(R)-5-methoxy-1,2,3,4-tetrahydro-naphthalen-1-ylmethyl]-N-methylamine;

N-[2-(N-Methyl-2,3-dihydro-1H-indol-5-yl)-ethyl]-N-[(R)-5-methoxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]-N-methylamine;

5-{2-[((R)-5-Methoxy-1,2,3,4-tetrahydro-naphthalen-1-ylmethyl)methyl-amino]-ethyl}-1,3-dihydro-indol-2-one;

N-[2-(N-Trifluoromethanesulfonamido-1,3-dihydroisoindol-5-yl)ethyl]-N-[(R)-5-methoxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]-N-methylamine;

N-[2-(N-Ethanesulfonamido-1,3-dihydroisoindol-5-yl)ethyl]-N-[(R)-5-methoxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]-N-methylamine;

N-[2-(Benzofuran-7-yl)ethyl-N-[(R)-8-fluoro-5-methoxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]-N-methylamine;

N-[2-(Benzofuran-6-yl)ethyl-N-[(R)-8-fluoro-5-methoxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]-N-methylamine;

N-[2-(2,3-Dihydrobenzofuran-6-yl)ethyl-N-[(R)-5-hydroxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]-amine;

N-[2-(2-Indolinone-6-yl)ethyl-N-[(R)-5-methoxy-1,2,3,4-tetrahydro-naphthalen-1-ylmethyl]-N-methylamine;

N-[2-(N-Methanesulfonamido-1,3-dihydroisoindol-5-yl)ethyl-N-[(R)-5,6-methylenedioxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]-N-ethylamine;

N-[2-(2,3-Dihydrobenzofuran-6-yl)ethyl-N-[(R)-5,6-methylenedioxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]-N-ethylamine;

N-[2-(N-Methanesulfonamido-1,3-dihydroisoindol-5-yl)ethyl-N-[(R)-5-methoxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]-N-ethylamine;

N-[2-(N-Methanesulfonamido-1,3-dihydroisoindol-5-yl)ethyl-N-[(R)-8-fluoro-5-methoxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]-N-methylamine ;

N-[2-(N-Methanesulfonamido-1,3-dihydroisoindol-5-yl)ethyl-N-[(R)-5,6-methylenedioxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]-N-methylamine;

N-[2-(2,3-Dihydrobenzofuran-6-yl)ethyl]-N-[(R)-5-ethoxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]-N-methylamine;

N-[2-(2,3-Dihydrobenzofuran-7-yl)ethyl]-N-[(R)-5-methoxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]-N-methylamine;

N-[2-(Benzofuran-7-yl)ethyl]-N-[(R)-5-methoxy-1,2,3,4-tetrahydro-naphthalen-1-ylmethyl]-N-methylamine;

N-[2-(2,3-Dihydrobenzofuran-7-yl)ethyl]-N-[(R)-5,6-methylenedioxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]-N-methylamine;

N-[2-(N-Methanesulfonamido-1,3-dihydroisoindol-5-yl)ethyl]-N-[(R)-5-ethoxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]-N-methylamine;

N-[2-(Quinolin-5-yl)ethyl]-N-[(R)-5-methoxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]-N-methylamine;

N-[2-(Quinolin-8-yl)ethyl]-N-[(R)-5-methoxy-1,2,3,4-tetrahydro-naphthalen-1-ylmethyl]-N-methylamine;

N-[2-(Quinolin-6-yl)ethyl]-N-[(R)-5,6-methylenedioxy-1,2,3,4-tetrahydro-naphthalen-1-ylmethyl]-N-methylamine;

N-[2-(Benzo[b]thien-3-yl)ethyl]-N-[(R)-5-methoxy-1,2,3,4-tetrahydro-naphthalen-1-ylmethyl]-N-methylamine;

N-[2-(Benzo[b]thien-2-yl)ethyl]-N-[(R)-5-methoxy-1,2,3,4-tetrahydro-naphthalen-1-ylmethyl]-N-methylamine;

N-[2-(Indol-3-yl)ethyl]-N-[(R)-5-methoxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]-N-methylamine;

N-[2-(N-Trifluoromethanesulfonamido-2,3-dihydroindol-6-yl)ethyl]-N-[(R)-5-methoxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]-N-methylamine;

N-[2-(2,3-Dihydrobenzo[b]thien-5-yl)ethyl]-N-[(R)-5,6-methylenedioxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]-N-methylamine;

N-[2-(N-Methanesulfonamido-2,3-dihydroindol-6-yl)ethyl]-N-[(R)-5,6-methylenedioxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]-N-methylamine ;

N-[2-(2,3-Dihydroindol-5-yl)ethyl]-N-[(R)-5,6-methylenedioxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]-N-methylamine;

N-[2-(Benzofuran-5-yl)ethyl]-N-[(R)-5,6-methylenedioxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]-N-methylamine;

N-[2-(2,2-Dioxo-1,3-dihydrobenzo[c]thien-5-yl)ethyl]-N-[(R)-5-methoxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]-N-methylamine;

N-[2-(2,2-Dioxo-1,3-dihydrobenzo[c]thien-5-yl)ethyl]-N-[(R)-5,6-methylenedioxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]-N-methylamine;

N-[2-(Benzofuran-7-yl)ethyl]-N-[(R)-5,6-methylenedioxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]-N-methylamine;

N-[2-(1,1-Dioxo-2,3-dihydrobenzo[b]thien-5-yl)ethyl]-N-[(R)-5-methoxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]-N-methylamine;

N-[2-(3-Methyl-benzofuran-5-yl)ethyl]-N-[(R)-5-methoxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]-N-methylamine;

N-[2-(2-Methyl-benzofuran-5-yl)ethyl]-N-[(R)-5-methoxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]-N-methylamine;

N-[2-(2,3-Dihydrobenzo[b]thien-5-yl)ethyl]-N-[(R)-5-methoxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]-N-ethylamine;

N-[2-(Benzofuran-6-yl)ethyl]-N-[(R)-5-methoxy-1,2,3,4-tetrahydro-naphthalen-1-ylmethyl]-amine;

N-[3-(2-(1,2-Benzisothiazolin-3-one-1,1-dioxide))propyl]-N-[(R)-5-methoxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]-N-methylamine;

N-[3-(2-(1,2-benzisothiazolin-3-one-1,1-dioxide))ethyl]-N-[(R)-5-methoxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]-N-methylamine;

N-[2-(2,3-Dihydrobenzofuran-6-yl)ethyl]-N-[(R)-5,6-methylenedioxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]-N-methylamine;

N-[2-(2,3-Dihydrobenzo[b]thien-5-yl)ethyl]-N-[(R)-5-ethoxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]-N-methylamine;

5-{2-[((R)-5,6-Methylenedioxy-1,2,3,4-tetrahydro-naphthalen-1-ylmethyl)methyl-amino]-ethyl}-1,3-dihydro-indol-2-one;

N-[2-(2-Chloro-benzothiazol-6-yl)-ethyl]-N-{(R)-5,6-methylenedioxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]-N-methylamine;

N-[2-(Benzothiazol-6-yl)-ethyl]-N-{(R)-5,6-methylenedioxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]-N-methylamine;

N-[2-(N-Methanesulfonamido-1,3-dihydroisoindol-5-yl)ethyl]-N-[(R)-5,6-methylenedioxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]-N-methylamine;

6-{2-[((R)-5-,6-Methylenedioxy-1,2,3,4-tetrahydro-naphthalen-1-ylmethyl)methyl-amino]-ethyl}-3H-benzoxazol-2-one;

N-[2-(2-Amino-benzothiazol-6-yl)-ethyl]-N-{(R)-5,6-methylenedioxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]-N-methylamine;

N-[2-(Benzoxazol-6-yl)-ethyl]-N-{(R)-5,6-methylenedioxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]-N-methylamine;

N-[2-(Benzo[b]thien-5-yl)ethyl]-N-[(R)-5,6-Methylenedioxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]-N-methylamine;

N-[2-(Benzofuran-6-yl)ethyl]-N-[(R)-5,6-methylenedioxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]-N-methylamine;

N-[2-(2,3-Dihydrobenzofuran-4-yl)ethyl]-N-[(R)-5-methoxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]-N-methylamine;

N-[2-(2,3-Dihydrobenzofuran-4-yl)ethyl]-N-[(R)-5,6-methylenedioxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]-N-methylamine;

6-{2-[((R)-5-Methoxy-1,2,3,4-tetrahydro-naphthalen-1-ylmethyl)methyl-

amino]-ethyl}-3H-benzoxazol-2-one;

215 5-{2-[((R)-5-Methoxy-1,2,3,4-tetrahydro-naphthalen-1-ylmethyl)methyl-amino]-ethyl}-3H-imidazol-2-one; and

5-{2-[((R)-5-Methoxy-1,2,3,4-tetrahydro-naphthalen-1-ylmethyl)methyl-amino]-ethyl}-3H-benzoxazol-2-one.

12. A composition for inhibiting serotonin uptake and antagonizing alpha-2 adrenoreceptors comprising a therapeutically effective amount of a compound of Claim 1 in combination with a pharmaceutically acceptable carrier.

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13. A method for inhibiting serotonin uptake and antagonizing alpha-2 adrenoreceptors in a mammal in need of such treatment comprising administering to the mammal a therapeutically effective amount of a compound of Claim 1.

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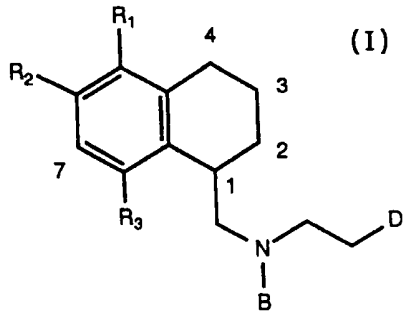

(57) Abstract

The present invention provides an amine compound of formula (I) or a pharmaceutically acceptable salt thereof which is an antagonist for alpha-2 adrenoreceptors and which inhibits serotonin (5-hydroxytryptamine, 5-HT) uptake.

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International application No.
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A. CLASSIFICATION OF SUBJECT MATTER

IPC(5) :C07D 301/79, 307/83, 307/87, 307/88, 333/54, 333/64, 333/72; A61K 31/34, 31/38
US CL :549/53, 54, 55, 58, 467; 514/ 443, 469, 470
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 549/53, 54, 55, 58, 467; 514/ 443, 469, 470

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAS Online Structure Search

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US, A, 5,140,040 (DEBERNARDIS ET AL) 18 August 1992, See entire document.	1-3, 8, 11-13
A	US, A, 4,722,933 (HORN) 02 February 1988. See entire document	1-3, 8, 11-13

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be part of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search 03 FEBRUARY 1993	Date of mailing of the international search report 24 FEB 1993
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer Emily Bernhardt Telephone No. (703) 308-1235

Form PCT/ISA/210 (second sheet)(July 1992)*

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US92/10794

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

Please See Extra Sheet.

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
Claims 1, 3, 11-13 (all in part) and 8

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US92/10794

BOX II. OBSERVATIONS WHERE UNITY OF INVENTION WAS LACKING
This ISA found multiple inventions as follows:

This application contains the following inventions or groups of inventions which are not so linked as to form a single inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

Group I, claim(s)1-3, 8, 11-13 (all in part), drawn to compounds, compositions and use where D= bensofuran, isobenzofuran, benzothienes, isobenzothienes and derivatives thereof, classified in Class 549, subclasses 53, 54, 58, 467; Class 514, subclasses 443, 469, 470..
Group II, claim(s) 1, 2, 7, 11-13 (all in part except 7), drawn to compounds, compositions and use where D = quinazolines, quinoxalines and derivatives thereof, classified in Class 544, subclasses 283, 353; Class 514, subclasses 249, 259.
Group III, claim(s) 1, 2, 10, 11-13 (all in part except 10), drawn to compounds, composition and use where D = benzopyrans and derivatives thereof, classified in Class 549, subclass 407; Class 514, subclass 457.
Group IV, claim(s) 1, 2, 6, 9, 11-13 (all in part) drawn to compounds, compositions and use where D = benzooxathioles and derivatives thereof, classified in Class 549, subclass 32; Class 514, subclass 439.
Group V, claim(s) 1, 2, 6, 9, 11-13 (all in part) drawn to compounds, compositions and use where D = benzo-1,3 and 1,2 -thiazoles and derivatives thereof, classified in Class 548, subclasses 164, 173, 179, 207, 209; Class 514, subclasses 367, 373
Group VI, claim(s) 1, 2, 6, 9, 11-13 (all in part) drawn to compounds, compositions and use where D = benzo- 1, 3 and 1, 2 oxazoles and derivatives thereof, classified in Class 514, subclasses 375, 379.
Group VII, claim(s) 1, 2, 6, 9, 11-13 (all in part) drawn to compounds, compositions and use where D = benzimidazoles and derivatives thereof, classified in Class 548, subclass 329, 331, 333; Class 514, subclass 394.
Group VIII, Claim(s) 1-3, 8, 11-13 (all in part) drawn to compounds, compositions and use where D = indoles, isoindoles and derivatives thereof, classified in Class 548, subclasses 472, 473, 481, 482, 486, 491, 503; Class 514, subclasses 415-418.
Group IX, claim(s) 1, 2, 5, 11-13 (all in part except 5) drawn to compounds, compositions and use where D = isoquinolines and quinolines and derivatives thereof, classified in Class 546, subclasses 149, 176; Class 514, subclasses 307, 311.
Group X, claim(s) 1, 2, 4, 5, 11-13 (all in part except 4) drawn to compounds, compositions and use where D = non-hetero rings, classified in Class 564, subclass 387; Class 514, subclass 655.
The above Groups lack unity of invention under PCT Rule 13 because the compounds of the respective groups are drawn to structurally dissimilar compounds as D varies in nature of hetero ring systems. Consequently the groups are classified separately in the U. S. as well as IPC Classification Systems. Each of the members of the groups are capable of being utilized alone and not in combination with the remaining groups. Furthermore, they would be expected to have independent utility - e.g. compounds of Group IX would be expected to be useful as cardiotonics when an oxo group is present on the hetro portion of the quinoline nucleus.